

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206333Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA 206333  
Product Name: Deoxycholic acid injection

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PMR Description: A safety assessment of deoxycholic acid treatment in subjects aged 65 years and older. This assessment is to be performed in the ongoing ATX-101-13-28 trial population of subjects aged 65 to 75 years. To the extent possible, all subjects should be continued through the planned end of the trial (even if a full course of treatment is not administered).

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PMR Schedule Milestones:

Trial Completion:	<u>04/30/2016</u>
Final Report Submission:	<u>09/30/2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

*At the EOP 2 meeting held on April 20, 2011 sponsor proposed to conduct separate Phase 3b trial in subjects older than 65 and the Division agreed. This trial is ongoing. The rationale was that this aesthetic treatment will be mostly used by younger population, therefore trials submitted for approval enrolled subjects 18-65 years.*

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

*Unwanted submental fat is condition that is present in elderly population therefore geriatric subpopulation should be represented sufficiently to permit the comparison of drug response in them to that of younger patients.*

*NDA review revealed only 16 treated subjects that were 65 years old which is insufficient number to conduct comparison to younger population. The risks associated with ATX treatment include marginal mandibular nerve injury and dysphagia.*

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

*A Multicenter, Double-blind, Placebo-controlled Efficacy and Safety Study of Deoxycholic Acid Injection for the Reduction of Localized Subcutaneous Fat in the Submental Area in Subjects 65 to 75 Years of Age*

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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MATTHEW E WHITE  
04/27/2015

TATIANA OUSSOVA  
04/27/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: March 20, 2015

To: Kendall Marcus, MD  
Director  
**Division of Dermatology and Dental Products (DDDP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Morgan Walker, PharmD, MBA  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Tara Turner, PharmD, MPH  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRADENAME (deoxycholic acid)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: NDA 206333

Applicant: Kythera Biopharmaceuticals, Inc.

## 1 INTRODUCTION

On May 12, 2014, Kythera Biopharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA) 206333 for TRADENAME (deoxycholic acid) injection with the proposed indication for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Dermatology and Dental Products (DDDP) on June 27, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (deoxycholic acid) injection.

## 2 MATERIAL REVIEWED

- Draft TRADENAME (deoxycholic acid) injection PPI received on May 12, 2014, and received by DMPP and OPDP on March 6, 2015.
- Draft TRADENAME (deoxycholic acid) injection Prescribing Information (PI) received on May 12, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 6, 2015.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/  
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MORGAN A WALKER  
03/20/2015

TARA P TURNER  
03/20/2015

BARBARA A FULLER  
03/23/2015

LASHAWN M GRIFFITHS  
03/23/2015

**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

**Memorandum**

**Date:** March 20, 2015

**To:** Matthew White  
Regulatory Project Manager  
Division of Dermatology and Dental Products (DDDP)

**From:** Tara Turner, Pharm.D., MPH  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Karen Rulli, Ph.D., Acting Team Leader, OPDP

**Subject:** **NDA 206333**  
**Deoxycholic acid injection, for subcutaneous use**

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On June 27, 2014, DDDP consulted OPDP to review the draft Package Insert labeling (PI), carton and container labeling, and Patient Package Insert (PPI) for Deoxycholic acid injection, for subcutaneous use (Deoxycholic acid) for the original NDA submission. We note that a proprietary name has not been finalized for this product at this time.

OPDP reviewed the proposed substantially complete version of the PI and PPI provided by DDDP via e-mail on March 6, 2015. OPDP also reviewed the revised carton and container labeling submitted to the electronic document room by the sponsor on February 9, 2015. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the PPI for Deoxycholic acid under separate cover. OPDP's comments on the PI and carton and container labeling are provided below.

Thank you for your consult. If you have any questions about OPDP's comments, please contact Tara Turner at 6-2166 or at [Tara.Turner@fda.hhs.gov](mailto:Tara.Turner@fda.hhs.gov).

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/s/  
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TARA P TURNER  
03/20/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Food and Drug Administration  
Office of New Drugs, Office of Drug  
Evaluation IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Review**

**Date:** February 13, 2015      **Consult Received:** January 13, 2015

**From:** Carol H. Kasten, MD, Medical Officer  
Division of Pediatric and Maternal Health,  
Office of Drug Evaluation IV (ODE IV)

**Through:** Tamara Johnson, MD, MS, Acting Team Leader  
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Acting Director  
Division of Pediatric and Maternal Health, ODE IV

**To:** Division of Dermatology and Dental Products

**Drug:** Kybella® (Deoxycholic Acid) injection, 10 mg/mL, NDA 206333  
IND 79726 (Dec 5, 2007) and IND (b)(4) (inactive Dec 30, 2010)

**Applicant:** Kythera Biopharmaceuticals, Inc.

**Proposed Indication:** The proposed indication is for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

**Subject:** Labeling Review

**Consult Request:** “The Division requests assistance with bringing the PI for deoxycholic acid injection into compliance with Final Pregnancy and Lactation Labeling Rule.”

## **INTRODUCTION**

On May 13, 2014, Kythera Biopharmaceuticals, Inc., submitted an original new drug application for Kybella, a synthetic deoxycholic acid injectable solution and a new molecular entity (NME). The drug is described as a cytolytic injectable with a proposed indication for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health - Maternal Health Team (DPMH-MHT) to review and revise sections of the Kybella labeling to bring it into compliance with the final Pregnancy and Lactation Labeling Rule.

## **BACKGROUND**

The Dermatologic and Ophthalmic Drugs Advisory Committee will meet on March 9, 2015, to review the Kybella NDA prior to approval as it is both a new molecular entity and a new class of drugs.

### Deoxycholic Acid and Drug Administration

Endogenous deoxycholic acid is a bile acid which emulsifies and solubilizes dietary fat to aid in its absorption. Once absorbed from the gut, endogenous deoxycholic either enters the enterohepatic circulation or is excreted in the feces. The applicant's current formulation of deoxycholic acid is not animal derived but is manufactured synthetically and is referred to henceforth, as synthetic deoxycholic acid (sDCA) to distinguish it from the endogenous form of the bile acid. The applicant had proposed that the pharmacologic class for sDCA be 'adipocytolytic;' however, the applicant's data demonstrated that sDCA has a cytolytic effect on muscle as well as adipose tissue. Per the Pharmacology Toxicology Review<sup>1</sup> the appropriate pharmacologic class for sDCA is 'cytolytic.'

Synthetic DCA is administered in 0.2 mL injections which are spaced 1cm apart into the subcutaneous fat in the preplatysmal plane using a 30 gauge (or smaller) 0.5 inch needle. The maximum dose in any treatment session is 100 mg (10 mL) or 50 injections repeated at intervals of not less than 4 weeks for up to a maximum of 6 treatment sessions.

### Clinical Pharmacology

Synthetic DCA acts as a detergent that chemically lyses and then dissolves the lipid bilayer of cell membranes. Clinical data discussed in the Clinical Pharmacology Review<sup>2</sup> demonstrated that following subcutaneous injection of the study drug, mean plasma concentrations of deoxycholic acid rose from approximately 200 ng/mL to 1000 ng/mL five minutes post injection. The median Tmax was 18 minutes with deoxycholic acid concentrations returning to baseline levels by 24 hours post-injection. Submitted preclinical rat data stated that the free fatty acids and triglycerides released by adipocyte lysis were eliminated in a manner similar to dietary fats.

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<sup>1</sup> Pharmacology/Toxicology NDA Review and Evaluation Primary Author: Jill Merrill, PhD; signed Dec 16, 2014. NDA 206333. DARRTS Reference ID: 3673206.

<sup>2</sup> Office of Clinical Pharmacology Review Primary Author An-Chi Lu, MS, PharmD, signed Dec 16, 2014. DARRTS Reference ID: 3673624

## DISCUSSION

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”<sup>3</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirement include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>4</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

### Database and Literature Review

#### *Pregnancy*

Synthetic DCA is an NME and therefore, the drug has not been reviewed in the Reprotox<sup>5</sup> TERIS<sup>6</sup> databases; however, Shepard’s Catalog<sup>7</sup> reviewed a study in which DCA was injected into pregnant rats’ peritoneum, uterine horns or amniotic sacs.<sup>8</sup> Only the intraperitoneal administration data could be relevant to human teratogenesis as it is the only exposure which might use the placenta for transport of the drug to the fetus, the likely mechanism of fetal exposure for the product under review. Intraperitoneal DCA administration may, however, also permit drug transport across the exterior surface of the rat uterine horns to the fetus. This extra-uterine to intrauterine movement of DCA would bypass the placenta and; therefore, this reference provides no data which may be used to predict human response to sDCA exposure.

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<sup>3</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>4</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products* (71 FR 3922; January 24, 2006).

<sup>5</sup> Reprotox® Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed February 3, 2014.

<sup>6</sup> TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women.  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidenceexpert/ND\\_PR/evidenceexpert/CS/](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidenceexpert/ND_PR/evidenceexpert/CS/) Accessed 3/21/2014.

<sup>7</sup> © 2014 Shepard's: A Catalog of Teratogenic Agents: An updated, automated version of Shepard's Catalog of Teratogenic Agents is distributed with TERIS. It's a comprehensive compilation of animal and human research on the teratogenicity of chemical and environmental agents. The Catalog contains information on over 2500 agents and includes many references for the Japanese as well as the American and European literature.

<sup>8</sup> Zimmer A, Susman I. Effects of Secondary Bile Acids on the Intrauterine Development in Rats; *Teratology* 1990;42:215-224.

There were four references in PubMed which discussed sDCA. One was a publication by the sponsor; the three other publications discussed use of sDCA but all of the women in all four references were required to use contraception during exposure to sDCA. Therefore, there are no published data on pregnant women exposed to sDCA.

Total bile acids can become elevated during pregnancy, typically in the last trimester, in a condition known as Intrahepatic Cholestasis of Pregnancy (ICP).<sup>9</sup> ICP is associated with serious adverse events such as fetal distress and premature delivery at total bile acid concentrations  $\geq 40 \mu\text{molar/L}$ .<sup>10</sup> The etiology of ICP is unknown but several mutations in genes controlling hepatocellular transport systems have been identified.<sup>11</sup> The prevalence of the disease differs significantly depending on the affected patient's genomic ancestry. Five percent of Latina women in Los Angeles have been reported to develop ICP whereas it occurs in less than one percent of Caucasian North American women.<sup>12,13</sup> The adverse effects of ICP are correlated with elevations of total bile acids with no data available on the individual bile acid concentrations. There is only a theoretical risk associated with elevation of one bile acid, DCA; no change to the Kybella labeling is recommended nor is any post-marketing surveillance.

#### *Lactation*

There is no review of sDCA in LactMed<sup>14</sup> and none of the four sDCA studies in adults noted above, accepted lactating women into the study. That said, endogenous DCA is absorbed from the gut as part of digestion and is normally found in blood. There are no data indicating the presence or absence of endogenous or synthetic DCA in human milk.

### **CONCLUSIONS**

DPMH-MHT attended the Late Cycle Meeting with the Division and applicant on January 27, 2015 and will attend the Advisory Committee Meeting in March, 2015.

#### Pregnancy Labeling

There are no human data on the effects of sDCA exposure during pregnancy. None of the publications reviewed provided data sufficient to be included in the Pregnancy (8.1)

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<sup>9</sup> Cunningham F, Leveno KJ, *et al.*. Hepatic, Biliary, and Pancreatic Disorders. In: Williams Obstetrics, Twenty-Fourth Edition. New York, NY: McGraw-Hill; 2013. . Accessed February 5, 2015. <http://accessmedicine.mhmedical.com/content.aspx?bookid=1057&Sectionid=59789200>

<sup>10</sup> Glantz A, Marschall H, Mattsson L. Intrahepatic Cholestasis of Pregnancy: Relationships Between Bile Acid Levels and Fetal Complication Rates. *Hepatology* 2004;40:467–74.

<sup>11</sup> Webb G, Elsharkawy A, Hirschfield G. The Etiology of Intrahepatic Cholestasis of Pregnancy. *Am J Gastroenterol* 2014; 109:85 – 88; doi: 10.1038/ajg.2013.437

<sup>12</sup> Lee R, Goodwin T, *et al.*. The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. *J Perinatology* (2006) 26, 527–532.

<sup>13</sup> See Cunningham, *et al.*.

<sup>14</sup> U.S. National Library of Medicine. National Institutes of Health. LactMed: A New NLM Database on Drugs and Lactation. (2013). Retrieved XYZ 2014 from <http://toxnet.nlm.nih.gov/cgi-bin/sis/search> .

labeling. The edits made to the Kybella labeling were recommended to comply with the PLLR guidelines.

### Lactation Labeling

There are no data to confirm or refute the presence of sDCA or endogenous DCA in human milk and the edits made to the Kybella Lactation (8.2) labeling focused on making it compliant with the PLLR guidelines.

## **RECOMMENDATIONS**

The following are the DPMH Maternal Health Team recommendations for the proposed labeling for Kybella in PLR format.

Language was provided in the following sections of the Kybella labeling:

## **HIGHLIGHTS OF PRESCRIBING INFORMATION**

ATX-101™ (deoxycholic acid) injection, for subcutaneous use

### **FULL PRESCRIBING INFORMATION: CONTENTS\***

#### **8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

#### **8 USE IN SPECIFIC POPULATIONS**

##### **8.1 Pregnancy**

###### *Risk Summary*

There are no adequate and well-controlled trials of ATX-101 in pregnant women to inform the drug-associated risk. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. In animal reproduction studies, no fetal harm was observed with the subcutaneous administration of deoxycholic acid to rats during organogenesis at doses up to 5 times the maximum recommended human dose (MRHD) of 100 mg [*see Data*].

###### *Data*

###### Animal Data

Embryofetal development studies have been performed in rats and rabbits using subcutaneous doses of deoxycholic acid administered during the period of organogenesis. For the basis of comparing animal to human doses, the MRHD is 1.7 mg/kg (100 mg/60 kg). No evidence of fetal harm was observed in rats at up to the highest dose tested (50 mg/kg) which is 5-fold higher than the MRHD of ATX-101 based on a mg/m<sup>2</sup>

comparison. However, missing intermediate lung lobe was noted in rabbits at all dose levels tested including the lowest dose (10 mg/kg) which is 2-fold higher than the MRHD of ATX-101 based on a mg/m<sup>2</sup> comparison. These effects may be related to maternal toxicity, which was also seen at all dose levels tested.

## **8.2 Lactation**

### *Risk Summary*

There is no information available on the presence of synthetic deoxycholic acid in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ATX-101 and any potential adverse effects on the breastfed child from ATX-101 or from the underlying maternal condition.

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/s/  
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CAROL H KASTEN  
02/13/2015

LYNNE P YAO  
02/17/2015

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

**DATE:** February 2, 2015

**TO:** Matthew White, Regulatory Project Manager  
Milena Lolic, M.D., Medical Officer  
David Kettl, M.D., Medical Team Leader  
Division of Dermatologic and Dental Products

**FROM:** Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 206333

**APPLICANT:** Kythera Biopharmaceuticals

**DRUG:** deoxycholic acid injection (ATX-101)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** For improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults

CONSULTATION REQUEST DATE: June 11, 2014  
 CLINICAL INSPECTION SUMMARY DATE: February 27, 2015  
 DIVISION ACTION GOAL DATE: April 27, 2015  
 PDUFA DATE: May 13, 2015

**I. BACKGROUND:**

The Applicant submitted this NDA to support the use of deoxycholic acid injection for the treatment of subjects seeking improvement in the appearance of moderate to severe convexity or fullness associated with submental fat.

The pivotal studies ATX-101-11-22 and ATX-101-11-23 entitled, “Multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of ATX-101 (sodium deoxycholate injection) versus placebo for the reduction of localized subcutaneous fat in the submental area” (the REFINE-2 study) and “Multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of ATX-101 (sodium deoxycholate injection) versus placebo for the reduction of localized subcutaneous fat in the submental area” (the REFINE-2 study), respectively, were inspected in support of this application.

Dr. Bhatia’s clinical site was selected for inspection because of the relatively large enrollment and the above average efficacy demonstrated in the study. (b) (6)

**II. RESULTS (by Site):**

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Bhatia, Ashish 2155 City Gate Lane, Suite 225 Naperville, IL 60563	ATX-101-11-23/ 531/ 16	18-26 Aug 2014	NAI
Monheit, Gary 2100 16th Avenue South, Suite 202 Birmingham, AL 35205	ATX-101-11-22/ 116/ 14	18-22 Aug 2014	NAI

Key to Classifications

NAI = No deviation from regulations.  
 VAI = Deviation(s) from regulations.  
 OAI = Significant deviations from regulations. Data unreliable.  
 Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Bhatia, Ashish  
2155 City Gate Lane, Suite 225  
Naperville, IL 60563

- a. **What was inspected:** At this site for Protocol ATX-101-11-23, 24 subjects were screened, and 16 subjects were enrolled and completed the study. Records reviewed for this study included informed consent forms for all screened subjects. Other records reviewed included, but were not limited to, site training logs, monitoring visit logs, test article accountability logs, delegation of authority logs, temperature logs, sponsor, investigator, monitor, and IRB correspondence, medical records, inclusion/exclusion criteria, adverse events, baseline determinations, case report forms (CRFs), and protocol deviations. Source records were compared against sponsor line listings, including a 100% review of primary and secondary endpoints (CR-SMFRS, PR-SMFRS, SMFMRI, PR-SMFIS) in addition to subject self-evaluations and SMSLG scores.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. The only discrepancy noted was for Subject 018 at Visit 4 (Treatment 3) where the data listing had a value of 4 for CR-SMFRS but the corresponding source document had a value of 1.
- c. **Assessment of data integrity:** Other than the discrepancy noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Monheit, Gary  
2100 16th Avenue South,  
Suite 202  
Birmingham, AL 35205

- a. **What was inspected:** At this site for Protocol ATX-101-11-22, 20 subjects were screened, 14 subjects were enrolled, and 13 subjects completed the study. The informed consent forms were reviewed for all study subjects. The records of eight randomly selected study subjects including three screen failures, were reviewed in depth. Review included but was not limited to inclusion/exclusion criteria, randomization dates, laboratory values, adverse events, case report forms, adverse event reporting, and drug randomization and accountability. Efficacy endpoints for five of the enrolled subject (assessments by both the clinical investigator and the study subject) were verified by a comparison between source documents, electronic case report forms, and line listings. Other records reviewed included delegation of authority, investigator training, laboratory certification, and sponsor, IRB, and monitor communications.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection; however, the unanticipated closing of the MRI facility responsible for imaging studies resulted in study subjects either not having baseline and end-of-study imaging done or for those in whom baseline imaging was done, the End of Study imaging was done well outside of the protocol-specified window (OOW). Specifically, for the 14 subjects that were enrolled in the study:

Subject #	Visit 9 End-of Study Window	Visit 9 Date of Imaging	Days Out-of Window
003	18 Dec 12	4 Feb 13	48
006	4 Dec 12	20 Feb 13	78
008	21 Dec 12	25 Feb 13	66
009	7 Aug 12	11 Feb 13	188
010	25 Dec 12	11 Feb 13	48
011	27 Dec 12	11 Feb 13	46
012	7 Jan 13	15 Feb 13	39
013	12 Nov 12	6 Feb 13	86
014	14 Jan 13	6 Mar 13	51
015	-	-	*
016	-	-	*
017	-	-	*
019	-	-	*
020	-	-	*

\*Baseline and End-of Study MRI imaging was not performed for these subjects because no MRI center was available at baseline to perform the imaging. Protocol exceptions were granted by the sponsor for enrollment of these subjects.

The substantial delay in collecting End-of Study MRI imaging data was discussed with Dr. Milena Lolic of the review division. Dr. Lolic indicated that the review division may choose to exclude this data from its assessment of the efficacy of the test article since the timing of the imaging was not in compliance with protocol-specified time frames.

Although protocol deviations were observed (i.e., OOW MRI assessments) for subjects due to the closure of the MRI facility, the “Major Protocol Deviations” data listing submitted by the sponsor to the NDA contained no protocol deviations (PD) for this site. The ORA investigator queried the site about documentation of PD data for these assessments. The ORA investigator did observe PD documentation by site personnel and (b) (4) (the monitoring CRO), although no examples were collected during the inspection. In an e-mail from the sponsor (J. Thomas, August 21, 2014) sent to the site in response to the ORA investigator’s query about PDs, the sponsor makes a distinction between “major” and “minor” protocol deviations. Only major protocol deviations defined by the sponsor as having impact on “subject safety or efficacy” were included in the clinical study report (CSR). The “major” protocol deviations were extracted by the sponsor (Kythera) from a separate, more comprehensive database maintained by (b) (4) and did not include OOW visits/assessments.

The review division should be aware that although the sponsor enumerates numerous “major” protocol deviations in Section 10.4 of the Clinical Study Report (e.g. study visit conducted outside of window, subject missed study visit, MRI not completed per protocol (e.g., collected out of window, sampling error, etc.)), Section 16.1.9 of the Clinical Study Report, Documentation of Statistical Methods, Section 5.2 Major Protocol Deviations, indicates that “major” protocol deviation information will be maintained separately from the eCRF and exports of these data will be delivered separately from the clinical datasets. “Deviations may include, but are not limited to the following: Inclusion/exclusion criteria deviations, randomization deviations, and terminations for lack of compliance.” In addition to OOW MRI assessments, there may be similar OOW visits for the physical measurements which were to be conducted every  $28\pm 5$  days. Such delays are unlikely to be limited to data from this one site.

- c. **Assessment of data integrity:** The review division may wish to re-examine study data to determine the extent to which OOW data was collected for efficacy assessments and whether this lack of compliance with protocol-specified timelines would affect the review division’s assessment of the safety and/or efficacy of the test article.

### **III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

The clinical sites of Drs. Monheit and Bhatia were inspected in support of this NDA. Dr. Monheit was not issued a Form FDA 483; however, the review division may wish consider the extent to which OOW findings may affect its assessment of the safety and/or efficacy of the test article. The final classification of Dr. Monheit’s inspection was No Action Indicated (NAI).

Dr. Bhatia was not issued a For FDA 483. The only discrepancy noted was for Subject 018 at Visit 4 (Treatment 3) where the data listing had a value of 4 for CR-SMFRS but the corresponding source document had a value of 1. Other than this discrepancy, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication. The final classification of Dr. Bhatia’s inspection was No Action Indicated (NAI).

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROY A BLAY  
02/04/2015

JANICE K POHLMAN  
02/17/2015

KASSA AYALEW  
02/17/2015

## STUDY ENDPOINT CONSULT REVIEW

<b>STUDY ENDPOINTS TRACKING NUMBER</b>	AT 2014-112
<b>IND/NDA/BLA NUMBER</b>	NDA 206333
<b>LETTER DATE/SUBMISSION NUMBER</b>	SDN-1
<b>PDUFA GOAL DATE</b>	
<b>DATE OF CONSULT REQUEST</b>	July 24, 2014
<b>REVIEW DIVISION</b>	DDDP
<b>MEDICAL REVIEWER</b>	Milena Lolic, MD
<b>TEAM LEADER, REVIEW DIVISION</b>	David Kettl, MD
<b>REVIEW DIVISION PM</b>	Matthew White
<b>STUDY ENDPOINTS REVIEWER(S)</b>	Sarrit Kovacs, PhD
<b>ASSOCIATE DIRECTOR, STUDY ENDPOINTS (ACTING)</b>	Elektra Papadopoulos, MD, MPH
<b>REVIEW COMPLETION DATE</b>	January 8, 2015
<b>ESTABLISHED NAME</b>	Deoxycholic acid
<b>TRADE NAME</b>	
<b>APPLICANT</b>	Kythera
<b>CLINICAL OUTCOME ASSESSMENT TYPE</b>	Clinician-reported outcome (ClinRO) and patient-reported outcomes (PROs)
<b>ENDPOINT(S) CONCEPT(S)</b>	Clinician-reported and patient-reported amount/size of submental fat (SMF); patient-reported visual and emotional impacts of SMF
<b>MEASURE(S)</b>	1. Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) 2. Patient-Reported Submental Fat Rating Scale (PR- SMFRS) 3. Patient-Reported Submental Fat Impact Scale (PR-SMFIS)
<b>INDICATION</b>	“ATX-101 is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with SMF in adults. A secondary objective is to demonstrate improvement in self-perceived visual and emotional impacts of submental fullness.”
<b>INTENDED POPULATION(S)</b>	Males and non-pregnant, non-lactating, females 18-65 years of age, inclusive, with undesirable submental convexity/fullness (moderate to severe submental fullness, convexity, or bulge associated with SMF) and a BMI of $\leq 40\text{kg/m}^2$ .

## Study Endpoints Review

Sarrit Kovacs, PhD

NDA 206333

Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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### A. EXECUTIVE SUMMARY

This Study Endpoints review is provided as a response to a request for consultation by the Division of Division of Dermatology and Dental Products (DDDP) regarding NDA 206333 regarding three clinical outcome assessments (COAs) that were used in two pivotal phase 3 studies in adult patients for improvement of the appearance of moderate to severe convexity or fullness associated with submental fat.

Two instruments, the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) and the Patient-Reported Submental Fat Rating Scale (PR- SMFRS), were used as co-primary endpoints for the measurement of undesirable submental convexity/fullness (moderate to severe submental fullness, convexity, or bulge associated with submental fat [SMF]).

The applicant included two co-primary efficacy endpoints in pivotal phase 3 (Studies 22 and 23):

- Composite 1-grade CR-SMFRS response and 1-grade PR-SMFRS response status at 12 weeks after the last treatment administration (i.e., the proportion of subjects who had at least a 1-grade improvement on both the CR-SMFRS and PR-SMFRS); and
- Composite 2-grade CR-SMFRS response and 2-grade PR-SMFRS response status at 12 weeks after the last treatment administration (i.e., the proportion of subjects who had at least a 2-grade improvement on both the CR-SMFRS and PR-SMFRS).

The third instrument, the Patient-Reported Submental Fat Impact Scale (PR-SMFIS), was used as a secondary endpoint for the measurement of self-perceived visual and emotional impacts of submental fullness.

The applicant seeks the following indication: “ATX-101™ (deoxycholic acid) injection is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.”

The review concludes that the evidence submitted by the applicant is sufficient to support the CR-SMFRS and PR-SMFRS in the context of a composite endpoint to measure the appearance of moderate to severe convexity or fullness associated with submental fat. However, the composite SMFRS appears to be adequate only to detect improvement, but not worsening because there appears to be very little (if any) difference between grades 3 and 4 on either the clinician or patient rating scale (i.e., photoguide and line drawing guide, respectively). While the PR-SMFRS is not an optimal instrument (because patients are likely to have difficulty viewing their own profiles in one handheld mirror), the instrument is acceptable within the context it was used. The CR-SMFRS and PR-SMFRS were used together in a composite; therefore, we are not relying only on one or the other.

## Study Endpoints Review

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Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR-SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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We agree that the PR-SMFIS total score is appropriate to support a claim in labeling as an assessment of the impact of treatment on how patients feel about their chin fat appearance, given that the instrument's measurement properties are adequate. There is some concern that certain individual items in the PR-SMFIS (e.g., "how much older do you look because of your chin fat" and "how much overweight do you look because of your chin fat") may be misleading if taken out of context. The drug is specifically for the treatment of fullness associated with submental fat in adults, (b)(4). However, the total PR-SMFIS score does not appear to be misleading given that all six items' change scores from baseline showed improvement with a similar magnitude of change. We conclude that the PR-SMFIS total score is appropriate to support a labeling claim as an assessment of the impact of treatment on how patients feel about their chin fat appearance. (b)(4)

## B. DIVISION'S QUESTIONS REGARDING APPLICANT'S SUBMISSION

Please find our responses to your three questions regarding the applicant's Clinical Outcome Assessment (COA) Evidence Dossier below:

Division Question 1: Has the applicant provided sufficient evidence to support CR-SMFRS and PR-SMFRS as primary endpoint measures in phase 3 studies?

### Response to Division Question 1:

**The review concludes that the evidence submitted by the applicant is sufficient to support the CR-SMFRS and PR-SMFRS in the context of a composite endpoint to measure the appearance of moderate to severe convexity or fullness associated with submental fat. However, the composite SMFRS appears to be adequate only to detect improvement, but not worsening because there appears to be very little (if any) difference between grades 3 and 4 on either the clinician or patient rating scale (i.e., photoguide and line drawing guide, respectively). While the PR-SMFRS is not an optimal instrument (because patients are likely to have difficulty viewing their own profiles in one handheld mirror), the instrument is acceptable within the context it was used. The CR-SMFRS and PR-SMFRS are being used together in a composite; therefore, we are not relying only on one or the other.**

Division Question 2: Has the applicant provided sufficient evidence that CR-SMFRS and PR-SMFRS are capable of identifying a 1-grade improvement suitable for labeling?

## **Study Endpoints Review**

Sarrit Kovacs, PhD

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Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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### **Response to Division Question 2:**

The Medical Officer Memo to File from May 23, 2011 expressed that the Division “consider a responder to be a subject who achieves an outcome score of a 0 or 1 and a two-grade improvement on both 5-point scales [CR-SMFRS and PR-SMFRS]” due to a number of concerns which have since been addressed by the applicant. For example, since the Memo to File, the applicant had included in the two pivotal phase 3 studies (22 and 23) a revised Frankfort plane grid to aid in standardizing the position of the head and neck.

The applicant provided anchor-based and distribution-based analyses derived from the phase trials to support the use of a 1-grade composite SMFRS responder definition as clinically meaningful.

The applicant’s argument for and evidence supporting the inclusion of a 1-grade improvement in labeling appears adequate.

Division Question 3: Has the applicant provided sufficient evidence to support the use of PR-SMFIS for efficacy claim?

### **Response to Division Question 3:**

Yes. The PR-SMFIS, which has been included as a secondary endpoint in phase 3 studies was developed in alignment with the PRO Guidance and the instrument’s measurement properties are adequate. There is some concern that certain individual items in the PR-SMFIS (e.g., “how much older do you look because of your chin fat” and “how much overweight do you look because of your chin fat”) may be misleading if taken out of context. The drug is specifically for the treatment of fullness associated with submental fat in adults, (b) (4). However, the total PR-SMFIS score does not appear to be misleading given that all six items’ change scores from baseline showed improvement with a similar magnitude of change. We conclude that the PR-SMFIS total score is appropriate for inclusion in labeling as an assessment of impact of treatment on how patients feel about their chin fat appearance. (b) (4)

[REDACTED]

## **Study Endpoints Review**

Sarrit Kovacs, PhD

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Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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## **C. STUDY ENDPOINT REVIEW**

Materials reviewed:

- Previous SEALD reviews for IND 079627
- DDDP/Sponsor meeting minutes
- DDDP clinical reviews
- Applicant's Clinical Outcome Assessment Evidence Dossier (the source of many of the tables included in this review)

### **1 CONTEXT OF USE (COU)**

#### **1.1 Target Study Population and Clinical Setting**

The target study population includes males and non-pregnant, non-lactating, females 18-65 years of age, inclusive, with undesirable submental convexity/fullness (moderate to severe submental fullness, convexity, or bulge associated with SMF) and a BMI of  $\leq 40 \text{kg/m}^2$ .

The key inclusion and exclusion criteria for the two pivotal phase 3 studies (Studies 22 and 23) is included in Appendix A of the present review.

Table 1 below has been reproduced from the applicant's COA Evidence Dossier:

## Study Endpoints Review

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Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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Table 1. Subject Baseline Demographics/Characteristics by Study

Demographic or Health Information	Study 22 (N=506)	Study 23 (N=516)
	Statistics or n (%)	Statistics or n (%)
Age (at randomization date, years)		
n	506	516
Mean (SD) <sup>1</sup>	49.5 (9.3)	47.9 (9.1)
Median	51.0	48.0
Min-Max <sup>1</sup>	19.0-65.0	19.0-65.0
Missing	0	0
Gender		
Male	85 (16.8%)	71 (13.8%)
Female	421 (83.2%)	445 (86.2%)
Missing	0	0
Race		
White	445 (87.9%)	444 (86.0%)
Black or African American	37 (7.3%)	45 (8.7%)
Asian	12 (2.4%)	9 (1.7%)
American Indian or Alaskan Native	2 (0.4%)	3 (0.6%)
Native Hawaiian or Pacific Islander	1 (0.2%)	4 (0.8%)
Multiple	2 (0.4%)	2 (0.4%)
Other	7 (1.4%)	9 (1.7%)
Ethnicity		
Hispanic or Latino	45 (8.9%)	79 (15.3%)
Not Hispanic or Latino	461 (91.1%)	437 (84.7%)

## Study Endpoints Review

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Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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Demographic or Health Information	Study 22 (N=506)	Study 23 (N=516)	
	Statistics or n (%)	Statistics or n (%)	
Weight (kg)			
n	505	514	
Mean (SD) <sup>1</sup>	81.1 (14.4)	80.8 (14.9)	
Median	80.3	79.4	
Min-Max <sup>1</sup>	45.8-128.4	51.2-160.1	
Missing/No response	1	2	
BMI (Kg/m <sup>2</sup> )			
n	505	514	
Mean (SD) <sup>1</sup>	29.2 (4.3)	29.3 (4.5)	
Median	28.9	28.7	
Min-Max <sup>1</sup>	19.4-40.0	18.2-45.6	
Missing/No response	1	2	
Fitzpatrick Skin Type			
I	25 (4.9%)	41 (7.9%)	
II	162 (32.0%)	132 (25.6%)	
III	180 (35.6%)	173 (33.5%)	
IV	96 (19.0%)	113 (21.9%)	
V	33 (6.5%)	42 (8.1%)	
VI	10 (2.0%)	15 (2.9%)	
Missing	0	0	

<sup>1</sup> BMI = body mass index; Max = maximum; Min = minimum; SD = standard deviation Source: Attachment A,

*Reviewer's comments: In response to an Agency concern that it was unclear why the sponsor was including patients with a score of 3 (neither satisfied nor dissatisfied with the appearance of the submental area) on the Subject Self Rating Scale (SSRS), the applicant had excluded patients with an SSRS score of 3 from phase 3 studies 22 and 23.*

## Study Endpoints Review

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### 1.2 Clinical Trial Design

- ATX-101-08-11 (Study 11): The primary objective of this study was to assess the intra-rater and inter-rater reliability of scores produced by the CR-SMFRS. There was no secondary objective and no investigational drug was tested or administered.  
ATX-101-09-15 (Study 15): The study was a phase 2b multicenter, randomized, double-blind, placebo-controlled study in which 129 patients were randomized to receive either up to 50 mg ATX-101, up to 100 mg ATX-101, or placebo in a 1:1:1 ratio (5 mg/mL:10 mg/mL:placebo). The primary objective of this phase 2b study was to evaluate the safety and efficacy of fixed concentrations of ATX-101 given in up to 50 0.2-mL injections in up to six treatment sessions, relative to placebo, when used for the reduction of SMF. A secondary objective of the study was to evaluate the psychometric performance and interpretability of the CR-SMFRS, PR-SMFRS, and PR-SMFIS instruments. The patients included in Study ATX-101-09-15 were males and females from 18 to 65 years of age (inclusive), with stable body weight and overall good health. The inclusion criteria for SMF were a score of 2 or 3 on the CR-SMFRS and SMF considered undesirable by the patient, as characterized by a score of 0, 1, 2, or 3 on the Subject Self Rating Scale (SSRS).
- ATX-101-11-22 (Study 22): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.
- ATX-101-11-23 (Study 23): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.

See Appendix A for more information on pivotal phase 3 Studies 22 and 23.

### 1.3 Endpoint Positioning

The applicant included two co-primary efficacy endpoints in pivotal phase 3 Studies 22 and 23:

- Composite 1-grade CR-SMFRS response and 1-grade PR-SMFRS response status at 12 weeks after the last treatment administration (Visit 9)
- Composite 2-grade CR-SMFRS response and 2-grade PR-SMFRS response status at 12 weeks after the last treatment administration (Visit 9)

The following Endpoint Model was reproduced from the applicant's COA Evidence Dossier:

## Study Endpoints Review

Sarrit Kovacs, PhD

NDA 206333

Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR-SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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Table 2. Primary and Secondary Efficacy Endpoints Model for ATX-101

Concept	Endpoint	Measurement Basis
<b>Primary</b>		
Amount/size of SMF (as reflected by submental convexity/fullness)	→ Composite 1-grade SMFRS response rate at 12 weeks after last treatment: proportion of subjects who have at least a 1-grade improvement on both the CR-SMFRS and the PR-SMFRS	ClinRO & PRO
	→ Composite 2-grade SMFRS response rate at 12 weeks after last treatment: proportion of subjects who have at least a 2-grade improvement on both the CR-SMFRS and PR-SMFRS	
<b>Secondary</b>		
Amount/size of SMF	→ MRI volume response rate at 12 weeks after last treatment: proportion of subjects who have at least a 10% reduction in SMF volume	MRI
Impact of submental fullness on subjects' perceptions associated with visual and emotional attributes.	→ Improvement from baseline to 12 weeks after last treatment in the self-perceived impacts of submental fullness (both visual and emotional) as assessed by the PR-SMFIS Total Scale score	PRO

Note: ClinRO=clinician-reported outcome; CR-SMFRS=Clinician-Reported Submental Fat Rating Scale; MRI=magnetic resonance imaging; PRO=patient-reported outcome; PR-SMFIS=Patient-Reported Submental Fat Impact Scale; PR-SMFRS=Patient-Reported Submental Fat Rating Scale; SMF=submental fat

### 1.4 Labeling or promotional claim(s) based on the COA

The following text has been reproduced from the applicant's proposed annotated label regarding the indication for ATX-101:

#### 1 INDICATIONS AND USAGE

**ATX-101<sup>TM</sup>** (deoxycholic acid) injection is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

**Study Endpoints Review**

Sarrit Kovacs, PhD

NDA 206333

Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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The following table has been reproduced from the applicant’s proposed label. The results are from the pooled data from pivotal phase 3 Studies 22 and 23 for the two co-primary composite endpoints.

**Table 2:** <sup>(b) (4)</sup>  $\geq 1$  Grade and  $\geq 2$  Grade Composite Clinician and Patient Response 12 Weeks After Final Treatment



The table content is redacted with a grey box. A (b) (4) redaction code is present in the top right corner of the redacted area.

The following figure has been reproduced from the applicant’s proposed annotated label. The results are from the pooled data from pivotal phase 3 Studies 22 and 23 for the CR-SMFRS and PR-SMFRS separately (i.e., not as a composite endpoint).

**Figure 4**



## Study Endpoints Review

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Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR-SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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The following figure has been reproduced from the applicant's proposed annotated label. The results are from the pooled data from pivotal phase 3 Studies 22 and 23 for the PR-SMFIS.



*Reviewer's comments: We agree that the PR-SMFIS total score is appropriate to support a claim in labeling as an assessment of the impact of treatment on how patients feel about their chin fat appearance.*

## 2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

The following figure and tables were reproduced from the applicant's COA Evidence Dossier:

- Figure 1 depicts the conceptual model
- Table 3 includes the links between the labeling claims, measurement concepts and instruments
- Table 3 depicts the conceptual framework

## Study Endpoints Review

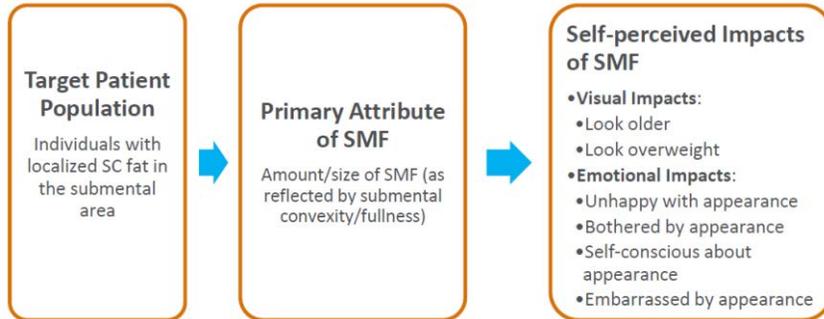
Sarrit Kovacs, PhD

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Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR-SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

Figure 1. ATX-101 Conceptual Model



Note: SC=subcutaneous; SMF=submental fat

Table 3. Link between Claims, Measurement Concepts, and Instruments

Claim	SMF Attribute (Measurement Concept)	Instrument
Primary: ATX-101 is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.	Amount/size of SMF (as reflected by submental convexity/fullness)	CR-SMFRS
		PR-SMFRS
Supportive: ATX-101 reduces the negative impact of submental fullness on subjects' perceptions associated with visual and emotional attributes.	Visual attributes associated with subjects' perceived submental fullness: <ul style="list-style-type: none"> <li>• Look older</li> <li>• Look overweight</li> </ul> Emotional attributes associated with subjects' perceived submental fullness: <ul style="list-style-type: none"> <li>• Unhappy</li> <li>• Bothered</li> <li>• Self-conscious</li> <li>• Embarrassed</li> </ul>	PR-SMFIS

Note: CR-SMFRS=Clinician-Reported Submental Fat Rating Scale; PR-SMFIS=Patient-Reported Submental Fat Impact Scale; PR-SMFRS=Patient-Reported Submental Fat Rating Scale; SMF=submental fat

## Study Endpoints Review

Sarrit Kovacs, PhD

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Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR-SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

Table 4. Conceptual Framework for the CR-SMFRS, PR-SMFRS, and PR-SMFIS

Measurement Instrument/Concept	Item Wording	Response Options
<b>CR-SMFRS</b>		
Amount/size of SMF (as reflected by submental convexity/fullness)	(Clinicians will be trained to assess amount/size of SMF on the CR-SMFRS scale [see right])	0=Absent submental convexity: No localized submental fat evident 1=Mild submental convexity: Minimal, localized submental fat 2=Moderate submental convexity: Prominent, localized submental fat 3=Severe submental convexity: Marked, localized submental fat 4=Extreme submental convexity
<b>PR-SMFRS</b>		
Amount/size of SMF (as reflected by submental convexity/fullness)	“How much fat do you have under your chin right now?”	0=No chin fat at all 1=A slight amount of chin fat 2=A moderate amount of chin fat 3=A large amount of chin fat 4=A very large amount of chin fat
<b>PR-SMFIS</b>		
Happy with appearance of chin	“How happy are you with the appearance of your chin fat?”	0=Not happy at all to 10=Extremely happy <sup>1</sup>
Bothered with appearance of chin	“How bothered are you by the appearance of your chin fat?”	0=Not bothered at all to 10=Extremely bothered
Self-conscious of appearance of chin	“How self-conscious are you about the appearance of your chin fat?”	0=Not self-conscious at all to 10=Extremely self-conscious
Embarrassed about appearance of chin	“How embarrassed are you about the appearance of your chin fat?”	0=Not embarrassed at all to 10=Extremely embarrassed
Look older because of chin	“How much older do you look because of your chin fat?”	0=Not older at all to 10=Very much older
Look overweight because of chin	“How much overweight do you look because of your chin fat?”	0=Not overweight at all to 10=Extremely overweight

Note: CR-SMFRS=Clinician-Reported Submental Fat Rating Scale; PR-SMFIS=Patient-Reported Submental Fat Impact Scale; PR-SMFRS=Patient-Reported Submental Fat Rating Scale; SMF=submental fat

<sup>1</sup>PR-SMFIS Item 1 is reverse scaled relative to the other PR-SMFIS items and this is accounted for in the composite PR-SMFIS Total Scale score.

## 3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

### 3.1 Clinician-Reported Submental Fat Rating Scale (CR-SMFRS)

- Instrument**

The Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) is a clinician-reported outcome (ClinRO) instrument that provides a single-score rating of SMF amount/size (recorded as a whole number). Clinicians evaluate the submental convexity, or the extent to which the submental chin is bulged, bowed, or rounded outward. Submental convexity is characterized by the presence and appearance of localized SMF size. The rating scale

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includes a single 5-point scale (0=“absent submental convexity” to 4=“extreme submental convexity”) with relevant descriptors for each of the 5 grades. A copy of the CR-SMFRS including the revised Frankfort Plane guide used in pivotal phase 3 Studies 22 and 23 is included in Appendix B of this review.

- User manual

The applicant included a copy of the CR-SMFRS user manual, original Frankfort plane guide, and photoguide as part of the Concept Elicitation Interview Report beginning on page 176 of 2212 of their COA Evidence Dossier (Appendix A of Attachment B of the applicant’s dossier), which have been reproduced in Appendices C, D, and E of the present review, respectively.

- Timing, data collection method and mode of administration

The CR-SMFRS is administered at clinic visits. Scores are assigned by a trained clinician following a clinical evaluation of the patient, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; and observation of pronation, supination, and lateral movement of the head. A score is assigned at screening to determine eligibility for study participation, at treatment visits prior to the administration of injections, and at follow-up visits. The primary post-treatment follow-up assessment was typically at the visit 12 weeks after last treatment (i.e., Visit 9 for studies that allowed up to six treatments and Visit 7 for studies that allowed up to four treatments). The score is determined using the definitions in the rating scale, with representative photographs associated with each score serving as a guide, and the final scoring determination made while the patient’s head is in the Frankfort plane posture; detailed patient positioning instructions were included only in pivotal Studies 22 and 23 (see Appendix B of this review).

Additionally, the protocols for pivotal phase 3 Studies 22 and 23 and for open-label phase 3b Study 26 specified that all patient-reported assessments should be completed before the clinician-reported assessments, including the CR-SMFRS, (protocols for EU phase 3 Studies 16 and 17 indicated that patient assessments should be completed after the clinician assessments), and all the study protocols, in order to minimize bias, specified that clinicians were not to disclose either previous or current clinician-reported assessment results (including the CR-SMFRS score) to the patient.

- Scoring algorithm

As indicated in Appendix B of this review, the CR-SMFRS is a five-point rating scale with response options scored from 0 to 4 (as indicated, clinicians refer to a set of photographs associated with each score and SMF description to help standardize responses).

- Training method/materials

No training materials were found submitted by the applicant.

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*Reviewer's comments: This reviewer assumes that the photoguide and user manual reproduced in this review in Appendices C and E from the applicant's Concept Elicitation Interview Report are the final versions.*

### 3.2 Patient-Reported Submental Fat Rating Scale (PR-SMFRS)

- Instrument

The Patient-Reported Submental Fat Rating Scale (PR-SMFRS) is a PRO instrument that provides a single-score rating of the amount/size of SMF (scored as a whole number). The amount/size of SMF is operationalized via patient evaluation of their perceived amount of "chin fat." Patients select one of the five descriptors to classify the perceived amount/size of their chin fat. During administration of the PR-SMFRS, patients are given a copy of the instrument and a standard, non-magnifying mirror to assist in the rating. Patients are instructed to think about the submental chin area and to look in the mirror to evaluate only that area. The patient's response is matched to the corresponding five-point scale (0="No chin fat at all" to 4="A very large amount of chin fat"). A copy of the PR-SMFRS is included in Appendix F of this review.

- User manual

No user manual was found submitted by the applicant.

- Timing, data collection method and mode of administration

The PR-SMFRS is self-administered assessment completed by the patient with only limited instructions or assistance of study personnel. The PR-SMFRS is administered at specified clinic visits; if treatment is scheduled for the visit in question, the instrument is administered prior to treatment. Patients are given a copy of the instrument and a standard, non-magnifying mirror is made available to the patient to assist in the rating. In pivotal studies, patients were instructed to position their heads in a manner similar to that described for CR-SMFRS assessment (i.e., Frankfort plane) before looking in the mirror. Patients are instructed to think about the submental chin area and to look in the mirror to evaluate only that area. Investigators may remind the patients exactly where on the face the treatment was (or will be) administered, and that only treated areas are expected to change with treatment (i.e., the area below the chin). If the patient has difficulty reading or understanding the PR-SMFRS, investigators are instructed to give no recommendations or advice to the patient regarding what answer to select, or on what to base their answers, apart from orienting the patient to focus only on the submental chin area.

Each of the protocols for pivotal phase 3 Studies 22 and 23, EU phase 3 Studies 16 and 17, and open-label phase 3B Study 26 indicated that patients should complete the PR-SMFRS assessment first, followed by the PR-SMFIS and then other patient questionnaires.

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- Scoring algorithm  
The PR-SMFRS is a five-point rating scale; response options are assigned a score from 0 to 4 (0=“No chin fat at all” to 4=“A very large amount of chin fat”).
- Training method/materials  
No training materials were found submitted by the applicant.

### 3.3 Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

- Instrument  
The Patient-Reported Submental Fat Impact Scale (PR-SMFIS) is a PRO questionnaire designed to evaluate the impact that submental fullness has on patients’ perceptions of happiness, bother, embarrassment and self-consciousness due to their “chin fat,” as well as how much they perceive their “chin fat” to make them look older or overweight. When administering the PR-SMFIS, patients are given a copy of the instrument and a standard, non-magnifying mirror is made available to assist in the rating. Patients are instructed to think about the submental chin area and to look in the mirror to evaluate only that area. They are asked to respond to six items on an 11-point numeric rating scale where 0=no impact (“not at all”) and 10=extreme impact (“extremely”). For example, item 3 asks, “How self-conscious are you about the appearance of your chin fat?” and item 5 asks, “How much older do you look because of your chin fat?” A copy of the PR-SMFIS is included in Appendix G of this review.
- User manual  
No user manual was found submitted by the applicant.
- Timing, data collection method and mode of administration  
The PR-SMFIS is administered at specified clinic visits; if treatment is scheduled for the visit, the instrument is administered prior to treatment. During administration of the PR-SMFIS, patients are given a copy of the instrument and a standard, non-magnifying mirror to assist in the rating. Patients are instructed to think about the area under their chin and to look in the mirror to evaluate only that area. The study protocols indicate that patients should complete the PR-SMFRS assessment first, followed by the PR-SMFIS, and then other patient questionnaires. In order to minimize bias, clinicians were instructed to not disclose the CR-SMFRS score to the patient.
- Scoring algorithm  
The PR-SMFIS Total Scale score is defined as the average of the six individual item scores; however, because the first item’s response options are in the opposite direction from the other scores (i.e., for PR-SMFIS Item 1 [happy], a higher score characterizes a “better” outcome), it is calculated as the sum of 10 minus the first item score, plus the scores of the

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other five items, divided by 6. A higher PR-SMFIS Total Scale score represents a greater overall negative impact on patient self-perceptions due to SMF.

- Training method/materials

No training materials were found submitted by the applicant.

## 4 CONTENT VALIDITY

The determination of which attributes should populate the conceptual model (and, therefore, to be considered for measurement) of the CR-SMFRS, PR-SMFRS, and PR-SMFIS was an iterative process based on an examination of: (1) the published literature, (2) key opinion leader interviews, and (3) qualitative patient interviews with individuals interested in SMF treatment.

### 4.1 Content Validity of the CR-SMFRS

For the CR-SMFRS, content validity was established based on the following findings:

- The amount/size of SMF reflects the most important SMF attribute from the perspective of clinicians;
- The amount/size of SMF reflects what clinicians indicate they would like to see improved in response to effective SMF treatment; and
- The CR-SMFRS can be comprehended and meaningfully responded to by clinicians as a measure of SMF amount

To evaluate the preliminary CR-SMFRS, the instrument and a set of 50 additional photographs reflecting a wide distribution of amounts of SMF were provided to the same group of three experts used to generate the instrument, as well as two additional dermatologists who practice aesthetic medicine. This panel of five experts was asked to rate the additional photographs using the instrument and to provide comments regarding the utility and relevance of the descriptors in the instrument. Based on this exercise and subsequent review among members of the expert panel, a set of refinements were made in the scale descriptors. In addition, a set of two photographs per scale level were chosen for inclusion in the final instrument, based on concordant ranking among the expert reviewers.

*Reviewer's comments: The content validity of the CR-SMFRS has been reviewed in a previous SEALD review. However, we have the following comments regarding the NDA submission:*

1. *The photoguide for use with the CR-SMFRS was provided in a previous submission and reviewed in a previous SEALD review for IND 079726 (April 11, 2011; AT 2010-126). In reviewing the photoguide, this reviewer agreed that there are readily discernable differences in the appearance of submental bulge among most of the grades. However, the photoguide seems inadequate to detect worsening (i.e., a patient switching from grade 3 to 4) due to the striking similarity between the photos on the right hand side of*

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*the guide for grades 3 and 4; the photos appear to possibly be in reverse order and the left hand photo for grade 4 looks like a recessed chin.*

- 2. To address previously conveyed concerns, the applicant has added a grid in phase 3 studies 22 and 23 to help in determining neck and head positioning vertically as well as horizontally. The new instructions for using the updated Frankfort plane with the grid are included in Appendix B of this review. We agree that this grid aids in decreasing variability in clinician ratings.*
- 3. It is unclear why the sponsor had excluded patients with a grade of 4 on the CR-SMFRS (even though BMI may be up to 40). It is interesting to note that the applicant included patients with a grade of 4 in a supportive, but not pivotal, phase 3 study (Study 26).*

### 4.2 Content Validity of the PR-SMFRS

For the PR-SMFRS, content validity was established based on the following findings:

- The amount/size of SMF reflects the most important SMF attribute from the perspective of patients and clinicians;
- The amount/size of SMF reflects what patients and clinicians indicate they would like to see improved in response to effective SMF treatment; and
- The PR-SMFRS can be comprehended and meaningfully responded to by patients and clinicians as a measure of SMF amount.

Table 5 below includes the demographic and clinical characteristics of the concept elicitation interview sample of 29 patients (reproduced from the applicant's COA Evidence Dossier).

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Table 5. Concept Elicitation: Demographic and Clinical Characteristics

<b>DEMOGRAPHIC CHARACTERISTIC</b>	<b>Total N=29</b>
<b>AGE (Years):</b>	
- Mean (Std. Deviation)	43.7 (10.5) yrs
- Range	20-62 yrs
<b>GENDER</b>	
- Male	8 (27.6%)
- Female	21 (72.4%)
<b>MARITAL STATUS:</b>	
- Married or living as married	14 (48.3%)
- Widowed	---
- Separated	1 (3.4%)
- Divorced	4 (13.8%)
- Never married	10 (34.5%)
<b>EDUCATION:</b>	
- Elementary School	---
- High School	4 (13.8%)
- College	21 (72.4%)
- Graduate / Professional School	4 (13.8%)
<b>ETHNICITY:</b>	
- White	20 (69.0%)
- Black/ African American	2 (6.9%)
- Hispanic or Latino	5 (17.2%)
- Other: Half white & Half Hispanic	1 (3.4%)
- Other: Cape Verdien & Portuguese	1 (3.4%)
<b>EMPLOYMENT STATUS:</b>	
- Full-time	20 (69.0%)
- Part-time	2 (6.9%)
- Not Employed	3 (10.3%)
- Homemaker	1 (3.4%)
- Student	2 (6.9%)
- Retired	1 (3.4%)

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Clinical Characteristics	Total N=29
<b>SELF-RATED HEALTH:</b>	
- Excellent	9 (31.0%)
- Very Good	11 (37.9%)
- Good	9 (31.0)
- Fair	---
- Poor	---
<b>SUBJECT'S DESCRIPTION OF FAT UNDER CHIN:</b>	
- A large amount	4 (13.8%)
- A moderate amount	16 (55.2%)
- A small amount	6 (20.7%)
- None	3 (10.3%)
<b>SUBMENTAL FAT RATING BY CLINICIAN:</b>	
- 4	3 (10.3%)
- 3	9 (31.0%)
- 2	8 (27.6%)
- 1	7 (24.1%)
- 0	2 (6.9%)
<b>HEIGHT (inches):</b>	
- Mean (Std. Deviation)	66.7 (5.8)
- Range	61 - 74
<b>WEIGHT (pounds):</b>	
- Mean (Std. Deviation)	186.3 (46.8)
- Range	120.5 - 297

Table 6 below (reproduced from the applicant's COA Evidence Dossier) includes a summary saturation matrix which indicates that all relevant SMF concepts expressed by patients (both SMF attributes and impacts) emerged by no later than the third of the four interview cohorts (each cohort represents a "wave" of interviews, which were completed serially). In other words, saturation of concepts was achieved.

Table 6. Summary Saturation Matrix of SMF Attribute and Impact Concepts

	Cohort 1 (N=8)	Cohort 2 (N=7)	Cohort 3 (N=7)	Cohort 4 (N=7)
New SMF Attributes (n)	8	1	1	0
Proportion of Total SMF Attributes (%)	80%	10%	10%	0%
New SMF Impacts (n)	12	0	1	0
Proportion of Total SMF Impacts (%)	92%	0%	8%	0%

Note: SMF=submental fat

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Concept elicitation interview data indicated that patients considered two attributes of SMF as characteristic: amount/size of SMF and chin definition. As reflected in Table 7 below, all 29 patients characterized their SMF primarily based on its amount/size, and amount/size-related terminology characterized nearly 70% of all the language the patients used to describe their SMF. Though over 80% of patients also characterized their SMF based on chin definition, they did so less often, with chin definition-related language characterizing less than 30% of patient comments about their SMF. Two patients characterized their SMF in other ways (e.g., “aged chin” and “darkened skin” in the submental area). Results also suggested that patients were bothered by each of the reported SMF attributes, as seen in Table 7 below (reproduced from the applicant’s COA Evidence Dossier).

Table 7. Frequencies and Bothersomeness Ratings of Patient-reported SMF Attributes

SMF Attribute	Patients Reporting Attribute (n, [%])	Mentions* (n, [%])	Mean Bothersomeness Rating <sup>†</sup> (SD)
Amount/size of SMF	29 (100%)	57 (68.7%)	7.0 (1.73)
Chin definition	24 (83%)	24 (28.9%)	8.0 (1.59)
Other	2 (6.9%)	2 (2.4%)	6.83 (2.48)

SMF=submental fat; SD=standard deviation

\*N=83

<sup>†</sup>Scale from 1-10: 1=not bothersome; 10=extremely bothersome

The proposed PR-SMFRS items were evaluated for their readability and meaning via cognitive-debriefing interviews with 15 patients interested in SMF treatments. The methods and procedures used for these interviews mirrored those used during concept elicitation. Interviews were conducted and improvements made and tested iteratively, following which, the content of the instrument was finalized.

Table 8 below includes the demographic and clinical characteristics of the cognitive interview sample of 15 patients (reproduced from the applicant’s COA Evidence Dossier).

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Table 8. PR-SMFRS Cognitive Interviews: Demographic and Clinical Characteristics

	Total N=15 (100%)		Total N=15 (100%)
<b>AGE (Years):</b>		<b>SELF-RATED HEALTH</b>	
- Mean (Std. Deviation)	44.9 (12.0) yrs	- Excellent	6 (40.0%)
- Range	25-62 yrs	- Very Good	6 (40.0%)
<b>GENDER</b>		- Good	3 (20.0)
- Male	3 (20.0%)	- Fair	---
- Female	12 (80.0%)	- Poor	---
<b>MARITAL STATUS:</b>		<b>SUBJECT'S DESCRIPTION OF FAT UNDER CHIN</b>	
- Married or living as married	7 (46.7%)	- A large amount	1 (6.7%)
- Widowed	---	- A moderate amount	8 (53.3%)
- Separated	---	- A small amount	5 (33.3%)
- Divorced	5 (33.3%)	- None	1 (6.7%)
- Never married	3 (20.0%)	<b>SUBMENTAL FAT RATING BY CLINICIAN (CR-SMFRS)</b>	
<b>EDUCATION:</b>		- 4	2 (13.3%)
- Elementary School	---	- 3	4 (26.7%)
- High School	2 (13.3%)	- 2	5 (33.3%)
- College	9 (60.0%)	- 1	---
- Graduate / Professional School	4 (26.7%)	- 0	4 (26.7%)
<b>ETHNICITY:</b>		<b>HEIGHT (inches)</b>	
- White	12 (80.0%)	- Mean (Std. Deviation)	66.5 (3.8)
- Black/ African American	---	- Range	62 – 74.5
- Asian/Pacific Islander	1 (6.7%)	<b>WEIGHT (pounds)</b>	
- Hispanic or Latino	2 (13.3%)	- Mean (Std. Deviation)	190.0 (54.7)
<b>EMPLOYMENT STATUS:</b>		- Range	120 - 300
- Full-time	10 (66.7%)		
- Part-time	3 (20.0%)		
- Not Employed	1 (6.7%)		
- Student	1 (6.7%)		

*Reviewer's comments: It is important to note that the cognitive interview sample of 15 patients did not include any Black/African American patients. However, 2 of the 29 patients in the concept elicitation sample were Black/African American.*

*We have the following comments regarding the content validity of the the PR-SMFRS based on the applicant's NDA submission:*

- 1. It is helpful to see that the applicant has included a line drawing guide, the Patient-Reported Submental Fat Line-Drawing Assessment (PR-SMF-LD; Appendix H), as a supportive measure in pivotal phase 3 studies 22 and 23.*
- 2. There is some concern that the standardized line drawings might be difficult for patients to interpret because they have limited landmarks to orient patients.*
- 3. The PR-SMF-LD appears to be identical to the profiles of the photos in the photoguide that is used with the CR-SMFRS. Therefore, just as the photoguide for the CR-SMFRS is inadequate to detect worsening (i.e., a patient switching from grade 3 to 4) due to the*

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*similarity between the photos/profiles for grades 3 and 4, the PR-SMF-LD for use with the PR-SMFRS is also inadequate to detect worsening.*

4. *Finally, this line drawing guide does not get around the issue of patients likely having difficulty accurately viewing their own profiles for the assessment. It is unclear how one can accurately look at his/her profile in one handheld mirror. It would have been helpful if patients would have been instructed to take a hand mirror to a big standing mirror and use both mirrors simultaneously to see their profiles against a Frankfort plane grid or to have a profile photo taken of themselves using the Frankfort plane grid in the background.*
5. *Additionally, it appears that there is no training with patients to make sure that they are holding their heads in the right vertical and horizontal position.*

### 4.3 Content Validity of the PR-SMFIS

The sponsor conducted the following activities in the development of the PR-SMFIS:

- Review of literature, interviewing of clinicians, and interviewing patients with SMF
- Patients characterized the impact of SMF convexity/fullness in terms of how it makes them look (i.e., visual impacts, or looking overweight and older) and how it makes them feel (i.e., emotional impacts, or feeling self-conscious, unhappy, bothered, and embarrassed); and
- The PR-SMFIS can be comprehended and meaningfully responded to by patients as a measure of the appearance-related impacts of SMF.

In addition to attribute and treatment-expectation findings, patients reported the impacts of SMF amount/size in the concept elicitation interviews. SMF impacts reported by patients and their frequencies are summarized in Table 9 below (reproduced from the applicant's COA Evidence Dossier).

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Table 9. Frequencies of Patient-reported SMF Impacts

SMF Impact Attribute	Patients Reporting Attribute (n, [%])
Feel less attractive	24 (17%)
Self-conscious	21 (15%)
Photos	18 (13%)
Feel older	17 (12%)
Related to overweight	13 (9%)
Embarrassed	11 (8%)
Mirrors	8 (6%)
Try to conceal	7 (5%)
Depressing	6 (4%)
Self-esteem	5 (4%)
Other	5 (4%)
Don't like it	4 (3%)
Worry/stress	2 (1%)
Total	141

Note: SMF=submental fat

The proposed PR-SMFIS items were evaluated for their readability and meaning via cognitive-debriefing interviews with 15 patients interested in SMF treatments. The methods and procedures used for these interviews mirrored those used during concept elicitation. Interviews were conducted and improvements made and tested iteratively, following which, the content of the instrument was finalized.

*Reviewer's comments: We have the following comments regarding the content validity of the PR-SMFIS:*

- 1. We agree that the instrument's measurement properties are adequate, the total PR-SMFIS score does not appear to be misleading given that all six items' change scores from baseline showed improvement (b) (4) [redacted], and the age range, mean, and median for the two pivotal phase 3 studies (Studies 22 and 23) all appear reasonable in that the trials did not include only older patients and that younger patients were included as well.*
- 2. We conclude that the PR-SMFIS total score is appropriate for inclusion in labeling as an assessment of impact of treatment on how patients feel about their chin fat appearance. (b) (4) [redacted]*

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## 5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

### 5.1 Other Measurement Properties of the CR-SMFRS

The data from four studies (including two pivotal phase 3 studies) were used to evaluate the measurement properties of the CR-SMFRS (see Appendix A in the present review for more information on the phase 3 studies):

- ATX-101-08-11 (Study 11): The primary objective of this study was to assess the intra-rater and inter-rater reliability of scores produced by the CR-SMFRS. There was no secondary objective and no investigational drug was tested or administered.
- ATX-101-09-15 (Study 15): The primary objective of this phase 2b study was to evaluate the safety and efficacy of ATX-101, relative to placebo, when used for the reduction of SMF. A secondary objective of the study was to evaluate the psychometric performance and interpretability of the CR-SMFRS.
- ATX-101-11-22 (Study 22): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.
- ATX-101-11-23 (Study 23): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.

Results of the applicant's psychometric evaluation of the CR-SMFRS were included in their Phase 2 CR-SMFRS and PR-SMFRS Instrument Measurement Property Evaluation Report (beginning on page 690 of 2212 of the COA Evidence Dossier) and their ATX-101 Phase 3 COA Measurement Property Evaluation Report (beginning on page 1078 of 2212 of the COA Evidence Dossier).

#### Reliability:

Intra-rater and inter-rater reliability of the CR-SMFRS were characterized by both intraclass correlation coefficients (ICCs) and kappa estimates, respectively. Study 11's results were reviewed in a previous SEALD review (AT 2011-061). Because the CR-SMFRS is single-item questionnaire, internal consistency reliability was not applicable. Intra-rater reliability analysis was not conducted in phase 3.

Construct validity: The correlations between the CR-SMFRS, PR-SMFRS, and the PR-SMFIS items and total scale score, as well as problems and difficulties with appearance (particularly in the chin, neck, and face area) were hypothesized *a priori* (in the statistical analysis plan) to be positive. In Study 15 (phase 2), moderate to strong correlations were found between the CR-SMFRS and PR-SMFRS at baseline (Spearman correlation coefficient  $r=0.30$ ;  $p=0.001$ ) and follow-up (Spearman correlation coefficient  $r=0.51$ ;  $p<0.001$ ), indicating an expected conceptual

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overlap but also a difference in how clinicians and patients evaluate the amount/size of SMF. At baseline, similar and mostly moderate correlations (Spearman) were observed between the CR-SMFRS and PR-SMFRS for pivotal phase 3 Studies 22 ( $r=0.199$ ) and 23 ( $r=0.260$ ). Stronger correlations were seen at follow-up for pivotal phase 3 Studies 22 ( $r=0.564$ ) and 23 ( $r=0.543$ ).

In Study 15 (phase 2), the correlation between the CR-SMFRS and PR-SMFIS total scale score at baseline was moderately correlated ( $r=0.22$ ); item #6 (“How much overweight do you look because of your chin fat?”) was more strongly correlated ( $r=0.25$ ). The applicant explained that this was not surprising given that PR-SMFIS item #6 requires a visual assessment like the CR-SMFRS. At follow-up, the PR-SMFIS total scale score was more strongly correlated with CR-SMFRS (Spearman  $r=0.51$ ).

Similar correlation coefficients (Spearman), at both baseline and follow-up assessment, were observed in the phase 3 studies compared to phase 2. More specifically, moderate to strong correlations between the CR-SMFRS and PR-SMFIS in Studies 22 ( $r=0.470$ ) and 23 ( $r=0.500$ ) at follow-up.

Exploratory known-groups analysis was conducted only in phase 3 in order to examine the degree to which scores produced by the CR-SMFRS can distinguish among groups considered *a priori* to be clinically distinct. As a proxy for clinically distinct or “known” groups, patient severity categories based on SMF amount/size were defined by caliper and MRI measurement quartiles. In general, for Studies 22 and 23, the CR-SMFRS t-test results showed that mean scores were significantly different ( $p \leq 0.001$  across the SMF size groups (1<sup>st</sup> and 4<sup>th</sup> quartiles) as determined by both the caliper measurement and MRI. The results of the analyses by caliper and MRI measurement are both displayed in Table 10 below.

Table 10. Known-groups Differences in the CR-SMFRS, PR-SMFRS, and PR-SMFIS with Groups Based on Caliper/MRI Quartiles at Visit 9 (Studies 22 and 23)

Study*	Caliper Quartile	CR-SMFRS			PR-SMFRS			PR-SMFIS		
		n	M (SD)	p-value <sup>†</sup>	n	M (SD)	p-value <sup>†</sup>	n	M (SD)	p-value <sup>†</sup>
22	1	107	1.0 (0.78)	<0.001	107	1.2 (0.83)	<0.001	107	3.4 (2.58)	<0.001
	2	104	1.5 (0.81)		104	1.4 (0.69)		104	4.4 (2.52)	
	3	119	2.0 (0.86)		119	1.8 (0.82)		119	5.2 (2.52)	
	4	136	2.1 (0.74)		136	2.0 (0.85)		136	6.0 (2.26)	
23	1	97	1.0 (0.80)	<0.001	97	1.2 (0.90)	<0.001	97	3.7 (2.71)	<0.001
	2	110	1.5 (0.90)		110	1.4 (0.78)		109	4.2 (2.50)	
	3	109	1.8 (0.91)		109	1.7 (0.86)		109	5.2 (2.74)	
	4	135	2.2 (0.85)		135	2.0 (0.83)		135	5.5 (2.54)	

Note: CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; M = mean; PR-SMFIS = Patient-Reported Submental Fat Impact Scale; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; SD = standard deviation

\*For Studies 22, 23, and 26, means based on Visit 9; and for Studies 16 and 17, means based on Visit 7

<sup>†</sup>P-values are derived from a t-test testing for mean differences between Group 1 and Group 4

Source: Attachment A; Table 9.1.1 (for Studies 22 and 23) and Table 9.1 (for Studies 16, 17, and 26)

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Study	MRI Quartile	CR-SMFRS			PR-SMFRS			PR-SMFIS		
		n	M (SD)	p-value <sup>†</sup>	n	M (SD)	p-value <sup>†</sup>	n	M (SD)	p-value <sup>†</sup>
22	1	48	1.2 (0.88)	<0.001	48	1.3 (0.93)	<0.001	48	3.7 (2.72)	<0.001
	2	48	1.7 (0.80)		48	1.7 (0.88)		48	4.7 (3.06)	
	3	48	1.8 (0.77)		48	1.6 (0.74)		48	5.1 (2.64)	
	4	48	2.1 (0.88)		48	2.0 (0.85)		48	5.6 (2.07)	
23	1	49	1.3 (0.66)	<0.001	49	1.2 (0.81)	<0.001	49	3.8 (2.48)	0.007
	2	49	1.6 (0.82)		49	1.6 (0.89)		49	4.3 (2.70)	
	3	49	2.0 (0.68)		49	1.9 (0.96)		49	5.3 (2.68)	
	4	49	2.1 (0.84)		49	1.9 (0.75)		49	5.2 (2.52)	

Note: CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; M = mean; MRI = magnetic resonance imaging; PR-SMFIS = Patient-Reported Submental Fat Impact Scale; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; SD = standard deviation

<sup>†</sup>P-values are derived from a t-test testing for mean differences between Group 1 and Group 4

Source: Attachment A; Tables 9.1.2 for each indicated study

**Ability to detect change:** In Study 15 (phase 2), change in the CR-SMFRS score (between baseline and week 32) was strongly associated with change in PR-SMFRS and PR-SMFIS and moderately associated with change in MRI thickness and volume. The amount of change resulting from treatment was characterized by Cohen effect size (mean change score divided by standard deviation of the baseline score) as being a large effect of -1.28. The results from Studies 22 and 23 (phase 3) were comparable to those generated in the Study 15.

Table 11 below (reproduced from the applicant's COA Evidence Dossier) displays the change score correlation analysis for Studies 22 and 23. The change scores that were similar in nature were indeed well-correlated, with magnitudes typically between moderate and strong providing further support for the sensitivity to change of these scales.

Table 11. Spearman Rank Correlations for Change From Baseline to Visit 9 Scores for Concurrent Assessment Instruments for Study 22 (N=466) Directly Below and Study 23 (N=451) Below Study 22's Results

	CR-SMFRS	PR-SMFRS	PR-SMFIS	SSRS <sup>†</sup>	PR-SMF-LD	Caliper	MRI
CR-SMFRS	1.000						
PR-SMFRS	0.447	1.000					
PR-SMFIS	0.424	0.560	1.000				
SSRS <sup>†</sup>	-0.480	-0.609	-0.614	1.000			
PR-SMF-LD	0.482	0.527	0.508	-0.535	1.000		
Caliper	0.331	0.278	0.294	-0.288	0.273	1.000	
MRI	0.469	0.297	0.394	-0.397	0.419	0.471	1.000

<sup>†</sup>The SSRS instrument scores are directionally opposite those of the other scores; negative values are expected when the results are consistent; p<0.05 for all coefficients. Individual n's may vary due to missing values for some measures

CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; MRI = magnetic resonance imaging; PR-SMFIS = Patient-Reported Submental Fat Impact Scale; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; PR-SMF-LD = Patient-Reported Submental Fat Line Drawing assessment; SSRS = Subject Self Rating Scale

Source: Attachment A, Table 10.3 for Study 22

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	CR-SMFRS	PR-SMFRS	PR-SMFIS	SSRS <sup>†</sup>	PR-SMF-LD	Caliper	MRI
CR-SMFRS	1.000						
PR-SMFRS	0.529	1.000					
PR-SMFIS	0.498	0.641	1.000				
SSRS <sup>†</sup>	-0.510	-0.638	-0.648	1.000			
PR-SMF-LD	0.397	0.511	0.499	-0.467	1.000		
Caliper	0.421	0.278	0.330	-0.336	0.277	1.000	
MRI	0.349	0.323	0.285	-0.311	0.284	0.235	1.000

<sup>†</sup>The SSRS instrument scores are directionally opposite those of the other scores; negative values are expected when the results are consistent; p<0.05 for all coefficients. Individual n's may vary due to missing values for some measures

CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; MRI = magnetic resonance imaging; PR-SMFIS = Patient-Reported Submental Fat Impact Scale; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; PR-SMF-LD = Patient-Reported Submental Fat Line Drawing assessment; SSRS = Subject Self Rating Scale

Source: Attachment A, Table 10.3 for Study 23

## 5.2 Other Measurement Properties of the PR-SMFRS

The data from one phase 2b study and two pivotal phase 3 studies were used to evaluate the measurement properties of the PR-SMFRS:

- ATX-101-09-15 (Study 15): The primary objective of this phase 2b study was to evaluate the safety and efficacy of ATX -101, relative to placebo, when used for the reduction of SMF. A secondary objective of the study was to evaluate the psychometric performance and interpretability of the PR-SMFRS.
- ATX-101-11-22 (Study 22): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.
- ATX-101-11-23 (Study 23): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.

Results of the applicant's psychometric evaluation of the PR-SMFRS were included in their phase 2 CR-SMFRS and PR-SMFRS Instrument Measurement Property Evaluation Report and their ATX-101 phase 3 COA Measurement Property Evaluation Report of the COA Evidence Dossier.

### Reliability:

Test-retest reliability of the PR-SMFRS were characterized by an ICC. The results were reviewed in a previous SEALD review (AT 2011-061) and was acceptable. Test-retest reliability analysis was not conducted in phase 3.

Construct validity: The correlations between the PR-SMFRS, CR-SMFRS, and the PR-SMFIS items and total scale score, as well as problems and difficulties with appearance (particularly in the chin, neck, and face area) were hypothesized *a priori* (in the statistical analysis plan) to be

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positive. The correlations between the PR-SMFRS and PR-SMFIS at baseline were strong (Spearman  $r=0.54$ ) in Study 15 (phase 2). At follow-up, the PR-SMFIS total scale score was more strongly correlated with the PR-SMFRS (Spearman  $r=0.71$ ).

Similar correlation coefficients (Spearman), at both baseline and follow-up assessment, were observed in the phase 3 studies compared to phase 2. More specifically, strong correlations between the PR-SMFRS and PR-SMFIS in Studies 22 ( $r=0.715$ ) and 23 ( $r=0.747$ ) at follow-up;

Exploratory known-groups analysis was conducted only in phase 3 in order to examine the degree to which scores produced by the PR-SMFRS can distinguish among groups considered *a priori* to be clinically distinct. As a proxy for clinically distinct or “known” groups, patient severity categories based on SMF amount/size were defined by caliper and MRI measurement quartiles. In general, for Studies 22 and 23, the PR-SMFRS t-test results showed that mean scores were significantly different ( $p \leq 0.001$  across the SMF size groups (1<sup>st</sup> and 4<sup>th</sup> quartiles) as determined by both the caliper measurement and MRI. The results of the analyses by caliper and MRI measurement are both displayed in Table 10 above.

Ability to detect change: In Study 15 (phase 2), change in the PR-SMFRS score (between baseline and week 32) was strongly associated with change in PR-SMFIS total scale score and moderately associated with change in CR-SMFRS and MRI thickness and volume. The amount of change resulting from treatment was characterized by Cohen effect size as being a large effect of -1.66. The results from Studies 22 and 23 (phase 3) were comparable to those generated in the Study 15.

### 5.3 Other Measurement Properties of the PR-SMFIS

The data from one phase 2b study and two pivotal phase 3 studies were used to evaluate the measurement properties of the PR-SMFIS:

- ATX-101-09-15 (Study 15): The primary objective of this phase 2b study was to evaluate the safety and efficacy of ATX -101, relative to placebo, when used for the reduction of SMF. A secondary objective of the study was to evaluate the psychometric performance and interpretability of the PR-SMFIS.
- ATX-101-11-22 (Study 22): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.
- ATX-101-11-23 (Study 23): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.

Results of the applicant’s psychometric evaluation of the PR-SMFIS were included in their PR-SMFIS Instrument Measurement Property Evaluation Report using data from and their ATX-101 Phase 3 COA Measurement Property Evaluation Report.

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**Reliability:** Cronbach's alpha for the six PR-SMFIS items was 0.855 and would be 0.862 if item #5 ("How much older do you look because of your chin fat?"). However, the applicant did not remove that item from the measure. Similarly, the PR-SMFIS items showed strong internal consistency reliability in the pivotal phase 3 studies. Test-retest reliability for the total scale score was an ICC of 0.75 with a 95% confidence interval of 0.65-0.82 in Study 15. The ICCs for the individual items ranged from 0.52 to 0.75. Test-retest reliability analysis was not conducted in phase 3.

**Construct validity:** The correlations between the PR-SMFIS items and total scale score and SMF size, specifically the CR-SMFRS and PR-SMFRS, were hypothesized *a priori* (in the statistical analysis plan) to be positive. See Sections 5.1 and 5.2 above for these results.

Exploratory known-groups analysis was conducted only in phase 3 in order to examine the degree to which scores produced by the PR-SMFIS can distinguish among groups considered *a priori* to be clinically distinct. As a proxy for clinically distinct or "known" groups, patient severity categories based on SMF amount/size were defined by caliper and MRI measurement quartiles. In general, for Studies 22 and 23, the PR-SMFIS t-test results showed that mean scores were significantly different ( $p \leq 0.007$  across the SMF size groups (1<sup>st</sup> and 4<sup>th</sup> quartiles) as determined by both the caliper measurement and MRI. The results of the analyses by caliper and MRI measurement are both displayed in Table 10 above.

**Ability to detect change:** In Study 15 (phase 2), change in the PR-SMFIS total scale score (between baseline and week 32) was strongly associated with change in PR-SMFRS and CR-SMFRS and moderately associated with change in MRI thickness and volume. The amount of change resulting from treatment was characterized by Cohen effect size as being a large effect of -2.00. The results from Studies 22 and 23 (phase 3) were comparable to those generated in the Study 15.

*Reviewer's comments: The descriptive statistics for the week 32 PR-SMFIS data look acceptable, as do the item-item Pearson r correlations at baseline. The measurement properties of the PR-SMFIS look acceptable.*

## 6 INTERPRETATION OF SCORES

The applicant stated that based on their results (see Sections 6.1, 6.2, and 6.3 below for more detailed results for the CR-SMFRS, PR-SMFRS, and PR-SMFIS, respectively), a 1-grade change from baseline on the CR-SMFRS, a 1-grade change from baseline on the PR-SMFRS, and a 3-point change from baseline on the PS-SMFIS all separately constitute a meaningful treatment benefit (i.e. responder).

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As additional confirmation, the applicant conducted exploratory methods to evaluate the ability of *a priori* treatment responder definitions (i.e., endpoints), including composite 1- or 2-grade changes on the CR-SMFRS and PR-SMFRS as well as a 10% decrease in MRI volume, to identify patients who benefitted from treatment. Based on their results, the applicant concluded that a composite 1-grade improvement on the CR-SMFRS and PR-SMFRS characterizes a group of patients who experience their perceived SMF change as important and meaningful (based on global improvement anchors and measures of satisfaction).

Among patients who were PGIC improvers, 79.1% and 79.8% were categorized as 1-grade composite SMFRS responders, while 80.6% and 82.9% of patients who were PGIC non-improvers were categorized as 1-grade composite SMFRS non-responders for Studies 22 and 23, respectively. Similar findings were reported using the SGQ#3 and SSRS measures. In other words, self-reported improvers were likely to be 1-grade composite SMFRS responders, and self-reported non-improvers were likely to be 1-grade composite SMFRS non-responders.

To summarize, the applicant stated that the 1-grade composite SMFRS responder categorization captures the perspective of the patient with regard to their perceived benefit.

*Reviewer's comments: The applicant's argument for and evidence supporting the inclusion of a 1-grade improvement in labeling appears adequate.*

### 6.1 Interpretation of Scores from the CR-SMFRS

The data from four studies (including two pivotal phase 3 studies) were used to evaluate the interpretability of scores produced by the CR-SMFRS:

- ATX-101-08-11 (Study 11): The primary objective of this study was to assess the intra-rater and inter-rater reliability of scores produced by the CR-SMFRS. There was no secondary objective and no investigational drug was tested or administered.
- ATX-101-09-15 (Study 15): The primary objective of this phase 2b study was to evaluate the safety and efficacy of ATX -101, relative to placebo, when used for the reduction of SMF. A secondary objective of the study was to evaluate the psychometric performance and interpretability of the CR-SMFRS.
- ATX-101-11-22 (Study 22): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.
- ATX-101-11-23 (Study 23): Multicenter, randomized, double-blind, placebo-controlled pivotal phase study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.

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Results of the applicant’s psychometric evaluation of the CR-SMFRS were included in their Phase 2 CR-SMFRS and PR-SMFRS Instrument Measurement Property Evaluation Report and their ATX-101 Phase 3 COA Measurement Property Evaluation Report.

### Anchor-based method establishing clinically meaningful responder definition:

The Patient Global Impression of Change (PGIC) item (i.e., Subject Global Question 1 in ATX-101-09-15) administered at week 32 was selected *a priori* as an anchor measure to characterize patients into groups (i.e., no change, large positive change, or large negative change). The PGIC is included in Appendix I of the present review.

Table 12 below (reproduced from the applicant’s COA Evidence Dossier) summarizes changes in CR-SMFRS from baseline to week 32 in Study 15 relative to the *a priori* change groupings for patient responses to the PGIC (at week 32).

Table 12. Mean CR-SMFRS and PR-SMFRS Change Scores (Week 32-Baseline) by PGIC Anchor at Week 32

Patient Global Impression of Change <sup>1</sup> :	Change in CR-SMFRS <sup>2</sup>			Change in PR-SMFRS <sup>2</sup>		
	N <sup>3</sup>	Mean	SD	N	Mean <sup>3</sup>	SD
About the same	29	-0.24	0.51	28	-0.32	0.55
A little better	29	-0.59	0.78	28	-0.89	0.74
Moderately better	29	-0.52	0.57	27	-1.15	0.66
A great deal better	34	-1.12	0.77	34	-1.47	0.66

<sup>1</sup> No subject reported worsening on the PGIC (i.e., a little worse, moderately worse, or a great deal worse) at Week 32 (12 weeks post last treatment).

<sup>2</sup> Positive (+) mean change scores indicates worsening; negative (-) scores indicate improvement

<sup>3</sup> To be eligible for analyses, subject required CR-SMFRS or PR-SMFRS scores at Baseline and 12 weeks post last treatment and PGIC score at 12 weeks post last treatment.

The mean change from baseline in CR-SMFRS scores among patients who rated their SMF as “moderately better” was 0.52. The applicant concluded that because individual changes can only be recorded in whole numbers, they are submitting a criterion of a 1-point change on the CR-SMFRS as indicative of meaningful treatment benefit (from the perspective of the individual seeking SMF treatment).

The specific wording of the PGIC item in the pivotal phase 3 studies was the same as that used in Study 15 (phase 2). Results from Studies 22 and 23 supported the results from Study 15 (i.e., a 1-point change) as seen in Table 13 below.

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Table 13. Mean Change of Scores from Baseline to Follow-Up by PGIC Anchor Level

PGIC Anchor Level (SQG #1)	CR-SMFRS			PR-SMFRS			PR-SMFIS Total Scale score			SSRS			PR-SMF-LD		
	n	Mean change	p-value <sup>1</sup>	n	Mean change	p-value <sup>1</sup>	n	Mean change	p-value <sup>1</sup>	n	Mean change	p-value <sup>1</sup>	n	Mean change	p-value <sup>1</sup>
<b>Study 22 (n=466)</b>															
A great deal worse	2	0.50	-	2	0.50	-	1	-4.33	-	2	0.50	-	2	-0.50	-
Moderately worse	4	0.25	1.000	4	0.75	0.250	4	0.96	0.250	4	0.75	1.000	4	0.25	1.000
A little worse	10	-0.30	0.250	10	-0.40	0.219	10	-0.30	0.939	10	0.40	0.750	10	-0.20	0.766
About the same	155	-0.30	<0.001	155	-0.15	0.007	155	-0.64	<0.001	155	0.81	<0.001	155	-0.08	0.252
A little better	77	-0.75	<0.001	77	-0.70	<0.001	77	-1.69	<0.001	77	2.30	<0.001	77	-0.60	<0.001
Moderately better	97	-1.15	<0.001	97	-1.06	<0.001	97	-2.91	<0.001	97	3.37	<0.001	97	-1.18	<0.001
A great deal better	109	-1.47	<0.001	109	-1.50	<0.001	109	-5.38	<0.001	109	4.19	<0.001	109	-1.92	<0.001
Between-group p-values <sup>2</sup>	-	-	<0.001	-	-	<0.001	-	-	<0.001	-	-	<0.001	-	-	<0.001
<b>Study 23 (n=451)</b>															
A great deal worse	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
Moderately worse	5	-0.40	0.500	5	0.60	0.500	5	0.03	0.625	5	0.20	1.000	5	0.60	0.750
A little worse	17	-0.29	0.234	17	-0.06	1.000	17	0.04	0.791	17	0.53	0.213	17	0.12	0.754
About the same	137	-0.24	<0.001	137	-0.11	0.012	137	-0.41	0.001	137	0.80	<0.001	137	-0.05	0.536
A little better	75	-0.67	<0.001	75	-0.64	<0.001	74	-2.01	<0.001	75	2.13	<0.001	75	-0.51	<0.001
Moderately better	88	-1.13	<0.001	88	-1.14	<0.001	88	-3.46	<0.001	88	3.36	<0.001	88	-1.25	<0.001
A great deal better	120	-1.56	<0.001	120	-1.52	<0.001	120	-5.27	<0.001	120	4.15	<0.001	120	-1.69	<0.001
Between-group p-values <sup>2</sup>	-	-	<0.001	-	-	<0.001	-	-	<0.001	-	-	<0.001	-	-	<0.001

The applicant conducted supportive analyses to establish the 1-grade responder definition for the CR-SMFRS which showed similar results to the change scores by PGIC anchor seen above.

In conclusion, anchor-based methods employed on the two pivotal phase 3 data sets for Studies 22 and 23 confirmed the conclusion from the phase 2 analysis that a 1-grade change from baseline on the CR-SMFRS represents a meaningful treatment benefit (i.e., mean change score among patients who reported the fat under their chin as “moderately better” post-treatment).

*Reviewer’s comment: The CR-SMFRS cumulative distribution function (CDF) plots appear adequate.*

## 6.2 Interpretation of Scores from the PR-SMFRS

The data from one phase 2b study and two pivotal phase 3 studies were used to evaluate the interpretability of scores produced by the PR-SMFRS:

- **ATX-101-09-15 (Study 15):** The primary objective of this phase 2b study was to evaluate the safety and efficacy of ATX -101, relative to placebo, when used for the reduction of SMF. A secondary objective of the study was to evaluate the psychometric performance and interpretability of the PR-SMFRS.
- **ATX-101-11-22 (Study 22):** Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.
- **ATX-101-11-23 (Study 23):** Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.

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Results of the applicant's psychometric evaluation of the PR-SMFRS were included in their Phase 2 CR-SMFRS and PR-SMFRS Instrument Measurement Property Evaluation Report (beginning on page 690 of 2212 of the COA Evidence Dossier) and their ATX-101 Phase 3 COA Measurement Property Evaluation Report.

### Anchor-based method establishing clinically meaningful responder definition:

The Patient Global Impression of Change (PGIC) item (i.e., Subject Global Question 1 in ATX-101-09-15) administered at week 32 was selected *a priori* as an anchor measure to characterize patients into groups (i.e., no change, large positive change, or large negative change). The PGIC is included in Appendix I of the present review.

Table 12 above summarizes changes in PR-SMFRS from baseline to week 32 relative to the *a priori* change groupings for patient responses to the PGIC (at week 32). The mean change from baseline in PR-SMFRS scores among patients who rated their SMF as “moderately better” was 1.15 points. The applicant concluded that because individual changes can only be recorded in whole numbers, they are submitting a criterion of a 1-point change on the PR-SMFRS as indicative of meaningful treatment benefit (from the perspective of the individual seeking SMF treatment).

In addition, a supportive analysis using *a priori* criteria on the CR-SMFRS to classify patients as either treatment responders or non-responders was conducted. Responders were defined as achieving either a 1 scale point or 2 scale point change in CR-SMFRS score (from baseline to week 32). Results are displayed in Table 14 below.

Table 14. PR-SMFRS Mean (SD) of Baseline, Week 32, and Change Scores among Patients Categorized as Responders Based on CR-SMFRS Change

Responder Population Definition	Analysis Variable	N <sup>1</sup>	Baseline		Week 32		Change	
			Mean	SD	Mean	SD	Mean	SD
Change in CR-SMFRS of at least 2 scale points	PR-SMFRS	14	2.43	0.514	0.86	0.663	-1.57	0.852
Change in CR-SMFRS of at least 1 scale point	PR-SMFRS:	59	2.31	0.500	1.10	0.578	-1.20	0.689

The applicant concluded from these analyses that there is convergence that a 1-point change in PR-SMFRS is viewed as clinically meaningful by patients.

In conclusion, anchor-based methods employed on the two pivotal phase 3 data sets for Studies 22 and 23 confirmed the conclusion from the phase 2 analysis that a 1-grade change from

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---

baseline on the PR-SMFRS represents a meaningful treatment benefit (i.e., mean change score among patients who reported the fat under their chin as “moderately better” post-treatment).

*Reviewer’s comment: The PR-SMFRS CDF plots appear adequate.*

### 6.3 Interpretation of Scores from the PR-SMFIS

The data from one phase 2b study and two pivotal phase 3 studies were used to evaluate the interpretability of scores produced by the PR-SMFIS:

- ATX-101-09-15 (Study 15): The primary objective of this phase 2b study was to evaluate the safety and efficacy of ATX -101, relative to placebo, when used for the reduction of SMF. A secondary objective of the study was to evaluate the psychometric performance and interpretability of the PR-SMFIS.
- ATX-101-11-22 (Study 22): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.
- ATX-101-11-23 (Study 23): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.

Results of the applicant’s psychometric evaluation of the PR-SMFIS were included in their PR-SMFIS Instrument Measurement Property Evaluation Report (beginning on page 995 of 2212 of the COA evidence dossier) and their ATX-101 Phase 3 COA Measurement Property Evaluation Report.

#### Anchor-based method establishing clinically meaningful threshold:

The Patient Global Impression of Change (PGIC) item (i.e., Subject Global Question 1 in ATX-101-09-15) administered at week 32 was selected *a priori* as an anchor measure to characterize patients into groups (i.e., no change, large positive change, or large negative change). The PGIC is included in Appendix J of the present review.

Table 15 below (reproduced from the applicant’s COA Evidence Dossier) summarizes changes in PR-SMFIS from baseline to week 32 relative to the *a priori* change groupings for patient responses to the PGIC (at week 32).

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Table 15. PR-SMFIS Change Scores (Week 32-Baseline) by PGIC Anchor at Week 32

Patient Global Impression of Change <sup>1</sup> : Since the start of this study, how would you rate the fat under your chin right now?	Change in PR-SMFIS <sup>2</sup>		
	N <sup>3</sup>	M	SD
About the same	29	-0.82	1.63
A little better	29	-2.87	1.65
Moderately better	29	-3.43	2.14
A great deal better	34	-5.77	1.99

<sup>1</sup> No subject reported worsening on the PGIC (i.e., a little worse, moderately worse, or a great deal worse) at Week 32.

<sup>2</sup> Positive (+) mean change scores indicates worsening; negative (-) scores indicate improvement.

<sup>3</sup> Total Scale score (item 1 is reversed scored)

<sup>4</sup> To be eligible for analyses, subject required PR-SMFIS scores at Baseline and Week 32 and PGIC score at Week 32.

The mean change from baseline in PR-SMFIS scores among patients who rated their SMF as “moderately better” was 3.43. Therefore, the applicant concluded that an ATX-101 treatment responder is one whose PR-SMFIS total scale score changes at least approximately 3.43 points from baseline.

In conclusion, anchor-based methods employed on the two pivotal phase 3 data sets for Studies 22 and 23 confirmed the conclusion from the phase 2 analysis that a 3-point change from baseline on the PR-SMFIS represents a meaningful treatment benefit (i.e., mean change score among patients who reported the fat under their chin as “moderately better” post-treatment).

*Reviewer’s comment: The PR-SMFIS CDF plots appear adequate.*

## 7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Translations for each language followed the International Society for Pharmacoeconomics and Outcomes Research Task Force for Translation and Cultural Adaptation principles of good practice for translation and cultural adaptation of PRO measures, which adhered to the following step-wise process including:

- Two independent adaptation reviews of the original US English version and of the reconciled adaptation report;
- Evaluation of the adaptation review suggestions for content equivalence;
- Developer review of finalized adaptation review grid;
- Cognitive interviews with five respondents from the target language and patient population; and
- Final formatting and proofreading of translation.

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Table 32. List of Instrument Translations and Their Implementation by Phase 3 Study

Language (country)	Study 22	Study 23	Study 16	Study 17	Study 26
Dutch (Belgium)			X	X	
Dutch (Netherlands)			X <sup>a</sup>	X <sup>a</sup>	
English (Canada)	X	X			
English (United States)*	X <sup>b</sup>	X <sup>b</sup>			X
French (Canada)			X	X	
French (France)			X	X	
German (Germany)			X	X	
Italian (Italy)				X	
Spanish (Spain)			X	X	
Spanish (United States)	X <sup>c</sup>	X <sup>c</sup>			X <sup>c</sup>

\*Original version developed in English for United States

a Translation was only used if a Netherlander was enrolled at one of the Belgian centers

b Translation was only used if a Quebecois was enrolled at one of the Canadian centers

c Translation was only used if a Spanish speaking subject was enrolled at one of the US centers

Certificates of translation and linguistic validation were included in Appendix L of the applicant's COA evidence dossier.

Translated versions of the instruments were included in Appendix M of the applicant's COA evidence dossier.

## 8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

N/A

## 9 USER MANUAL

The user information for the CR-SMFRS is included in Appendix C and has been reviewed in a previous Study Endpoint review, where it was found to be adequate.

## 10 CLINICAL TRIAL PROTOCOL AND ANALYSIS PLAN

Two pivotal phase 3 studies conducted in the US and Canada were used to evaluate the measurement properties of the CR-SMFRS, PR-SMFRS, and PR-SMFIS:

- ATX-101-11-22 (Study 22): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.

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- ATX-101-11-23 (Study 23): Multicenter, randomized, double-blind, placebo-controlled pivotal phase 3 study of 2 mg/cm<sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.

With regard to multiplicity adjustment in Studies 22 and 23, the applicant stated the following: “Because both endpoints must occur simultaneously for the primary analysis to be satisfied and to have a successful outcome, there is a single test for the success of the trial. As described in the protocol and SAP, no adjustments to alpha were made in evaluating the 2 primary efficacy endpoints, as both were required to reach significance for the trial to be deemed a success. The significance of both primary endpoints was used as a gate-keeper for the analysis of the secondary endpoints, and the Bonferroni-Holm method was used to adjust alpha for the secondary endpoint analyses.”

The timepoint of interest was Visit 9, which was 12 weeks after treatment.

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## APPENDIX A - STUDIES 22 AND 23 WERE PIVOTAL PHASE 3 STUDIES

Table 1: Overview of Studies

Study Number	Study Design	Number of Subjects (Randomized)	Primary Assessments	Secondary / Additional Efficacy Assessments	Sites and Countries
Study 22 and Study 23	Multicenter, randomized, double-blind, placebo-controlled study of 2 mg/cm <sup>2</sup> ATX-101 (up to 100 mg) or placebo in a 1:1 ratio to evaluate the safety and efficacy of up to 6 treatment sessions of ATX-101.	506 (ITT) subjects in Study 22; ATX-101 = 256, Placebo = 250  516 (ITT) subjects in Study 23; ATX-101 = 258, Placebo = 258	CR-SMFRS  PR-SMFRS	PR-SMFIS  MRI Volume <sup>†</sup>  SSRS*  PR-SMF-LD*  SRA*  MRI Thickness*  Caliper Measures*  Subject Global Questions*	35 sites in the US and Canada in each study.
Study 16 and Study 17	Multicenter, randomized, double-blind, placebo-controlled study of 1 mg/cm <sup>2</sup> ATX-101, 2 mg/cm <sup>2</sup> ATX-101 or placebo in a 1:1:1 ratio to evaluate the safety and efficacy of up to 4 treatment sessions of ATX-101.	363 (ITT) subjects in Study 16; 1 mg/cm <sup>2</sup> = 120, 2 mg/cm <sup>2</sup> = 121, Placebo = 122  358 (ITT) subjects in Study 17; 1 mg/cm <sup>2</sup> = 120, 2 mg/cm <sup>2</sup> = 122, Placebo = 116,	CR-SMFRS  SSRS	PR-SMFRS  PR-SMFIS  SRA  DAS  BIQLI  Subject Global Questions  Caliper Measures	29 sites in the EU for Study 16; 29 sites in the EU for Study 17
Study 26	Multicenter, open-label study of 2 mg/cm <sup>2</sup> ATX-101 for the reduction of localized subcutaneous fat in the submental area in up to 6 treatment sessions.	165 subjects	Safety	CR-SMFRS  PR-SMFRS  PR-SMFIS  SSRS*  PR-SMF-LD*  SRA*  Subject Global Questions*  Caliper Measures*	18 sites in the US

Note: Not all of the secondary/additional assessments listed above were evaluated as part of the COA analysis; ATX-101 is the study drug name; BIQLI = Body Image Quality of Life Inventory; CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; DAS = Derriford Appearance Scale; ITT = intent to treat; MRI = magnetic resonance imaging; PR-SMFIS = Patient-Reported Submental Fat Impact Scale; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; PR-SMF-LD = Patient-Reported Submental Fat Line-Drawing assessment; SRA = Self Ratings of Attractiveness; SSRS = Subject Self Rating Scale; <sup>†</sup> MRI evaluations were performed in a subset of approximately 200 subjects at selected centers; \* Additional efficacy assessment

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Table 2: Key Subject Inclusion Criteria

Criterion Number	Key Descriptions	Studies 22 & 23	Studies 16 & 17	Study 26
1	Males and non-pregnant, non-lactating females 18 to 65 years of age, inclusive	X	X	X
2	SMF graded by the investigator using CR-SMFRS	2 or 3	2 or 3	2, 3, or 4
3	SMF graded by the subject as using the PR-SMFRS	2 or 3	Not applicable	2, 3, or 4
4	SSRS score assessing submental area dissatisfaction	0, 1, or 2	0, 1, 2, or 3	0, 1, or 2
5	History of stable body weight, in the judgment of the investigator, for at least 6 months before randomization	X	X	X
6	Expected to understand and comply with the visit schedule and all protocol-specified tests and procedures (implies fluency in written English)	X	X	X

Note: CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; SMF = submental fat; SSRS = Subject Self Rating Scale

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Table 3: Key Subject Exclusion Criteria

Criterion Number	Key Descriptions	Studies 22 & 23	Studies 16 & 17	Study 26
1	History of any intervention to treat SMF (e.g., liposuction, surgery, or lipolytic agents)	X	X	X
2	History of trauma associated with the chin or neck areas that may affect evaluation of safety or efficacy of treatment	X	X	X
3	Excess skin laxity (Submental Skin Laxity Grade or Skin Laxity Rating Scale rating of 4) or other anatomical feature (e.g., predominant subplatysmal fat, loose skin in the neck or chin area, prominent platysmal bands) that may interfere in the evaluation of SMF or result in an aesthetically unacceptable outcome	X	X	X
4	Evidence of any cause of enlargement in the submental area (e.g., thyroid enlargement, cervical adenopathy) other than localized SMF	X	X	X
5	BMI (kg/m <sup>2</sup> )	>40.0	>30.0	>40.0
6	History or current symptoms of dysphagia	X	Not applicable	X
7	Coagulation test results which indicate the presence of any clinically significant bleeding disorder	X	Not applicable	Not applicable
8	Treatment with radio frequency, laser procedures, chemical peels, or dermal fillers in the neck or chin area within 12 months before randomization	X	X	X
9	Treatment with botulinum toxin injections in the neck or chin area within 6 months before randomization	X	X	X
10	Previous participation in a Kythera-sponsored ATX-101 trial	X	X	X
11	For centers selected to conduct MRI evaluations, any subject who is unsuitable for MRI evaluation	X	Not applicable	Not applicable

Note: BMI = body mass index; MRI = magnetic resonance imaging; SMF = submental fat

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## APPENDIX B – CR-SMFRS INCLUDING REVISED FRANKFORT PLANE

### 8.2.1. Clinician-Reported Submental Fat Rating Scale (CR-SMFRS)

Score	Submental Fat Description
0	Absent Submental Convexity: No localized submental fat evident.
1	Mild Submental Convexity: Minimal, localized submental fat.
2	Moderate Submental Convexity: Prominent, localized submental fat.
3	Severe Submental Convexity: Marked, localized submental fat.
4	Extreme Submental Convexity.

#### CR-SMFRS Assessment Procedures

*The following was applicable to all of the studies:*

The CR-SMFRS score was based on the investigator’s clinical evaluation of the subject, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the head.

Each investigational center was provided with the CR-SMFRS book containing representative photographs for each score and a 2-inch by 2-inch grid poster that was placed on the wall, with the horizontal lines parallel to the floor, in the area where the assessments were conducted.

The score was determined using the definitions in the rating scale and representative photographs associated with each score. To maintain a consistent posture from which the scores were made, the final determination of the score was made while the subject’s head was in the Frankfort plane posture.

The score was recorded as a whole number. At the Screening visit, the score was determined in conjunction with the protocol entry criteria (eg, absence of loose skin, diffuse SMF, and prominent platysmal bands at rest that interfered with evaluation of localized fat).

*In Studies 22 and 23 (the pivotal Phase 3 studies), the following additional information was specified in regard to the Frankfort plane posture:*

The correct posture was achieved as in the example below using the following:

1. The subject was positioned to stand facing the rater’s left, approximately 1 foot in front of the grid.
2. The rater stood such that he or she could visualize the horizontal lines on the grid, parallel to the plane from the subject’s lower orbital arch of the eye to the cephalic margin of the tragus of the ear. This is the Frankfort plane.
3. While the subject was in the correct position relative to the horizontal plane, the rater visualized the vertical lines to line up with the tragus and the front of the subject’s

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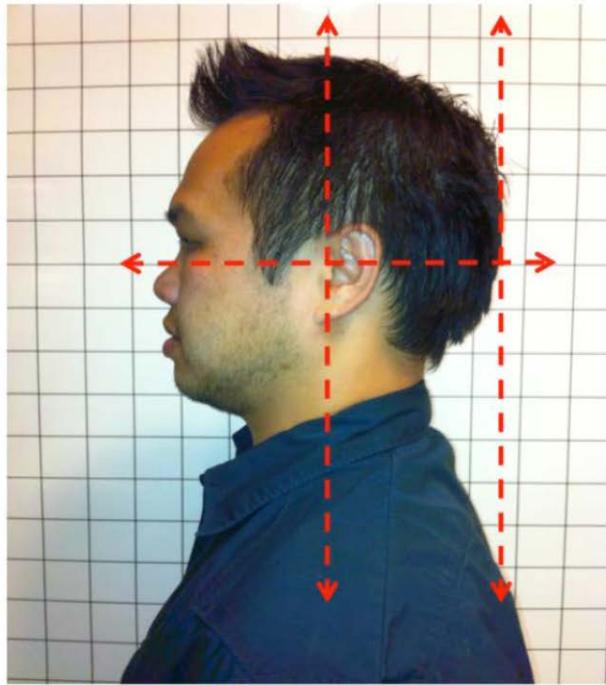
NDA 206333

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shoulder. Alternatively a vertical line could be used that aligned with the back of the subject's head on a plane slightly posterior to the subject's shoulder.



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## APPENDIX C – CR-SMFRS USER INFORMATION

# SMF Rating Scale

- SMF Score based on Investigator’s clinical evaluation of the subject including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the subject’s head.
- The final score is determined while the subject is in the Frankfort Plane posture, which is the posture depicted in the representative photographs.
- The score is determined using the definitions in the rating scale and representative photographs associated with each score. The score will be recorded as a whole number.
- At the screening assessment, the score is determined in conjunction with protocol entry criteria (*e.g.*, absence of loose skin, absence of diffuse submental fat, absence of prominent platysmal bands at rest that interfere with evaluation of localized fat).

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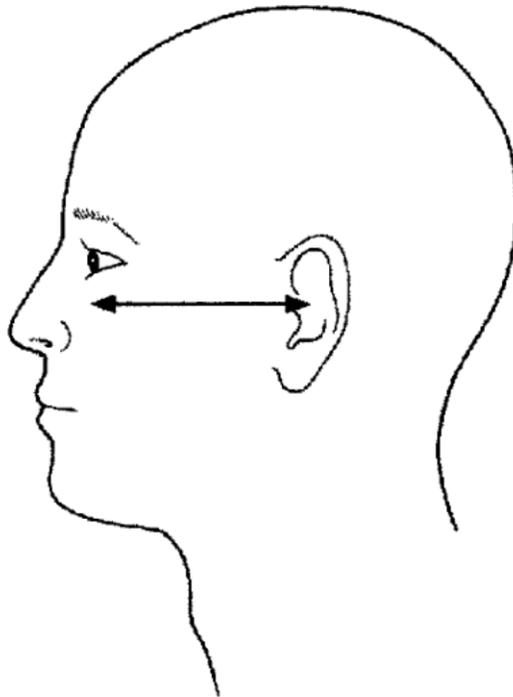
Deoxycholic acid

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## APPENDIX D - ORIGINAL FRANKFORT PLANE

# The Frankfort Plane



The Frankfort horizontal plane can be used to obtain accurate standardized facial views. The Frankfort plane lies on an imaginary horizontal line passing under the lower orbital arch to the cephalic margin of the tragus.

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## APPENDIX E – PHOTOGUIDE FOR USE WITH CR-SMFRS

### Score = 0

Absent Submental Convexity: No localized submental fat evident.



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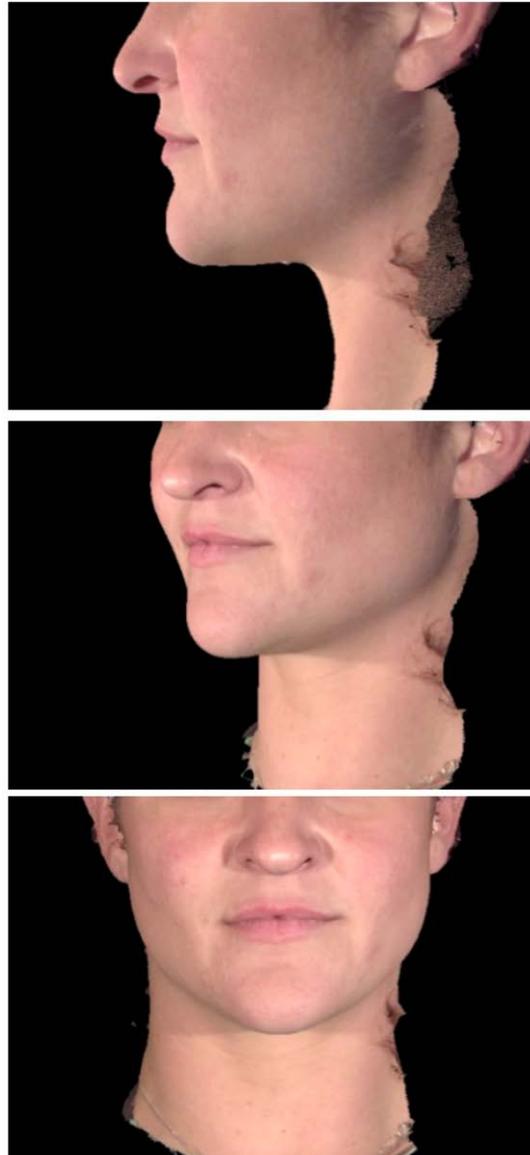
Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR-SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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### Score = 0

Absent Submental Convexity: No localized submental fat evident.



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**Score = 1**

Mild Submental Convexity: Minimal, localized submental fat.



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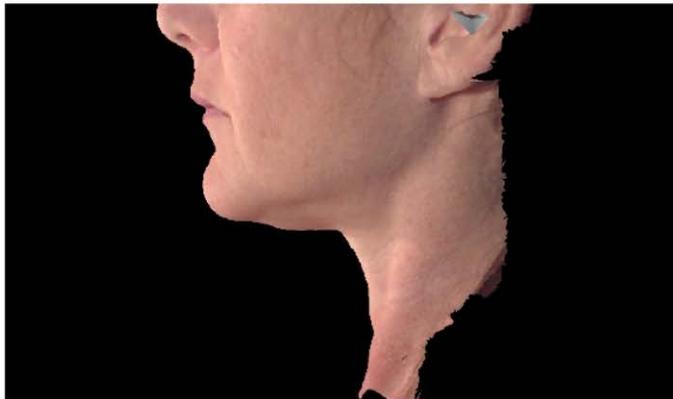
Deoxycholic acid

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**Score = 1**

Mild Submental Convexity: Minimal, localized submental fat.



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**Score = 2**

Moderate Submental Convexity: Prominent, localized submental fat.



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**Score = 2**

Moderate Submental Convexity: Prominent, localized submental fat.



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**Score = 3**

Severe Submental Convexity: Marked, localized submental fat.



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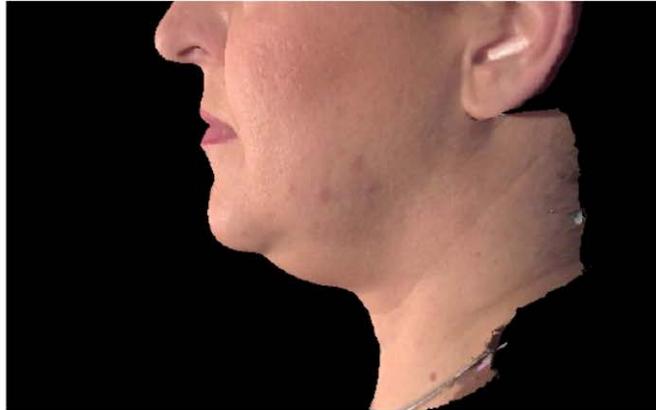
Deoxycholic acid

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**Score = 3**

Severe Submental Convexity: Marked, localized submental fat.



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**Score = 4**

Extreme Submental Convexity



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---

**Score = 4**

Extreme Submental Convexity



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## APPENDIX F – PR-SMFRS

### 8.2.2. Patient-Reported Submental Fat Rating Scale (PR-SMFRS)

The subject was instructed to position his or her head in a manner similar to that described for the CR-SMFRS assessment and asked to respond to the following:

*Please look in the mirror at **the area under your chin** to help you answer the following question:  
How much fat do you have under your chin right now?*

**How much fat do you have under your chin right now?**

Mark  in 1 box below

- |                          |                                 |
|--------------------------|---------------------------------|
| <input type="checkbox"/> | No chin fat at all              |
| <input type="checkbox"/> | A slight amount of chin fat     |
| <input type="checkbox"/> | A moderate amount of chin fat   |
| <input type="checkbox"/> | A large amount of chin fat      |
| <input type="checkbox"/> | A very large amount of chin fat |

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## APPENDIX G – PR-SMFIS

### 8.2.3. Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

Please look in the mirror at **the area under your chin** to help you answer the following questions:

1.

<b>How happy are you with the appearance of your chin fat?</b>
Mark <input type="checkbox"/> in 1 box below and do not mark between the boxes
Not happy at all <span style="float: right;">Extremely happy</span>
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10

2.

<b>How bothered are you by the appearance of your chin fat?</b>
Mark <input type="checkbox"/> in 1 box below and do not mark between the boxes
Not bothered at all <span style="float: right;">Extremely bothered</span>
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10

3.

<b>How self-conscious are you about the appearance of your chin fat?</b>
Mark <input type="checkbox"/> in 1 box below and do not mark between the boxes
Not self-conscious at all <span style="float: right;">Extremely self-conscious</span>
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10

**Study Endpoints Review**

Sarrit Kovacs, PhD

NDA 206333

Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

---

4.

<b>How embarrassed are you about the appearance of your chin fat?</b>	
Mark <input checked="" type="checkbox"/> in 1 box below and do not mark between the boxes	
Not embarrassed at all	E xtremely embarrassed
<input type="checkbox"/> — <input type="checkbox"/>	
0      1      2      3      4      5      6      7      8      9      10	

5.

<b>How much older do you look because of your chin fat?</b>	
Mark <input checked="" type="checkbox"/> in 1 box below and do not mark between the boxes	
Not older at all	Very much older
<input type="checkbox"/> — <input type="checkbox"/>	
0      1      2      3      4      5      6      7      8      9      10	

6.

<b>How much overweight do you look because of your chin fat?</b>	
Mark <input checked="" type="checkbox"/> in 1 box below and do not mark between the boxes	
Not overweight at all	Extremely overweight
<input type="checkbox"/> — <input type="checkbox"/>	
0      1      2      3      4      5      6      7      8      9      10	

## Study Endpoints Review

Sarrit Kovacs, PhD

NDA 206333

Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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## APPENDIX H – PR-SMF-LD (LINE DRAWINGS)

### 8.2.5. Standardized Line Drawings

#### Line Drawing Procedure:

Each subject was given 10 line drawings that included 2 example line drawings representing each of the 5 SMF scores. The drawings were printed on cards provided by Kythera; each card had a unique identifier. The profile depicted on each card was derived from the representative photograph's profile view in the CR-SMFRS. The unique identifiers were not associated with the CR-SMFRS score and were present only on the back of the card. Subjects were not provided with the CR-SMFRS score associated with the line drawings or any other written or verbal descriptions of the line drawing. The cards were provided to the subjects in a shuffled order. The subjects were asked to look at each line drawing and select the drawing that best represented how they believed their profile to be at the time. The subject was instructed that there is no incorrect answer; they were to have chosen the 1 drawing that best represents their profile.

The investigational center recorded the code corresponding to the selected line drawing. The code was matched to a grade (0 to 4).

The person presenting the cards to the subject read the following instructions to each subject: "Here are 10 profiles representing different shapes of the chin area. Please examine the cards and identify the line drawing that you believe is closest to your profile. If you are unsure, just select the overall closest match even if it is not perfect. There is no right and no wrong answer."

The line drawings that were presented are shown below, except that the SMF grades were not identified on the cards.

## Study Endpoints Review

Sarrit Kovacs, PhD

NDA 206333

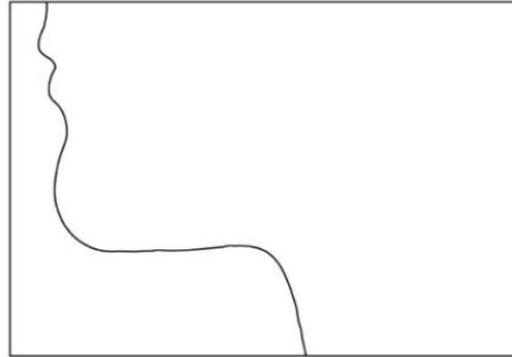
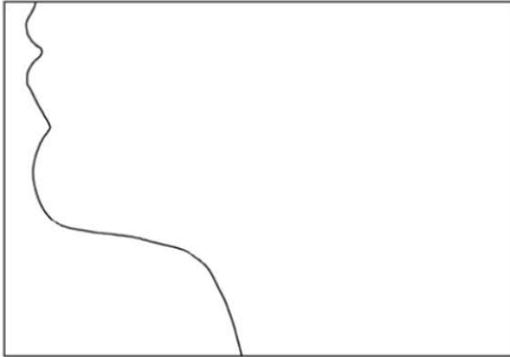
Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR-SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

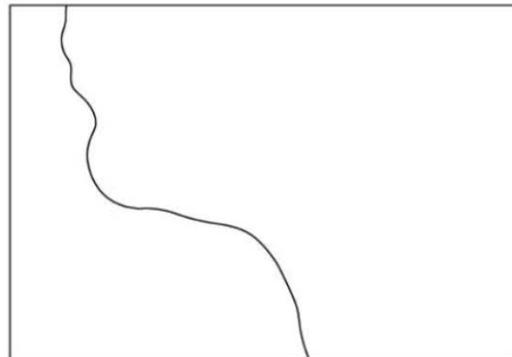
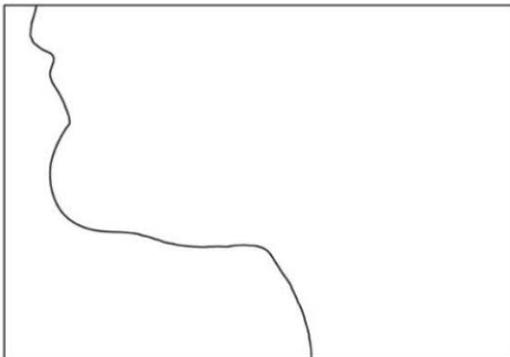
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### Line Drawing Cards:

Grade 0



Grade 1



**Study Endpoints Review**

Sarrit Kovacs, PhD

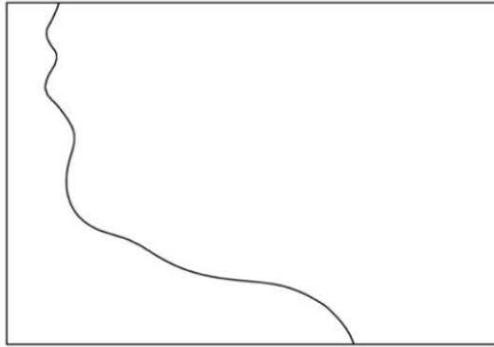
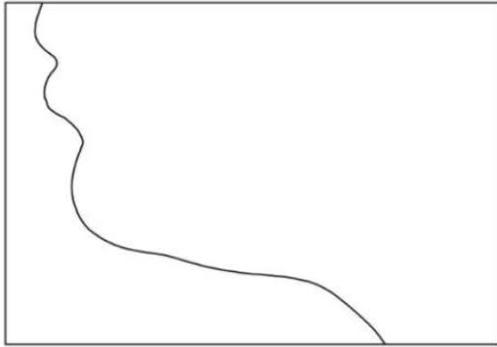
NDA 206333

Deoxycholic acid

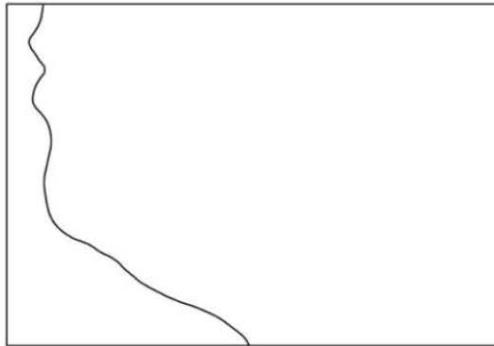
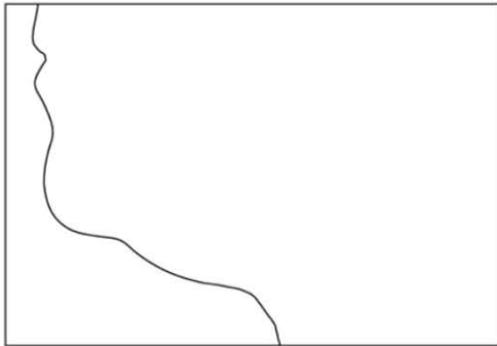
Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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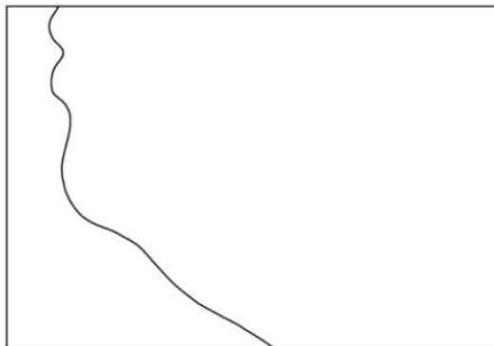
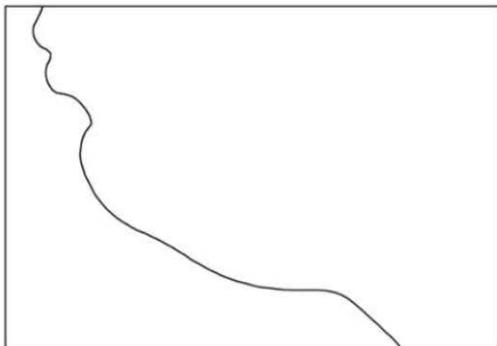
Grade 2



Grade 3



Grade 4



## Study Endpoints Review

Sarrit Kovacs, PhD

NDA 206333

Deoxycholic acid

Clinician-Reported Submental Fat Rating Scale (CR-SMFRS); Patient-Reported Submental Fat Rating Scale (PR- SMFRS); Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

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## APPENDIX I - PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

<b>Since the start of this study, how would you rate the fat under your chin right now?</b>	
Mark <input checked="" type="checkbox"/> in 1 box below	
<input type="checkbox"/>	A great deal worse
<input type="checkbox"/>	Moderately worse
<input type="checkbox"/>	A little worse
<input type="checkbox"/>	About the same
<input type="checkbox"/>	A little better
<input type="checkbox"/>	Moderately better
<input type="checkbox"/>	A great deal better

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/s/  
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SARRIT M KOVACS  
01/08/2015

ELEKTRA J PAPADOPOULOS  
01/09/2015

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## **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** December 04, 2014  
**Requesting Office or Division:** Division of Dermatology and Dental Products (DDDP)  
**Application Type and Number:** NDA 206333  
**Product Name and Strength:** Deoxycholic Acid Injection, 20 mg/2 mL (10 mg/mL)  
**Product Type:** Single ingredient product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Kythera Biopharmaceuticals  
**Submission Date:** May 13, 2014  
**OSE RCM #:** 2014-1243  
**DMEPA Primary Reviewer:** Carlos M Mena-Grillasca, RPh  
**DMEPA Team Leader:** Kendra Worthy, PharmD

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## 1 REASON FOR REVIEW

As part of the evaluation for NDA 206333, DDDP requested DMEPA evaluate the proposed container labels, carton labeling, and Full Prescribing Information for Deoxycholic Acid for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – n/a
Previous DMEPA Reviews	C
Human Factors Study	D – n/a
ISMP Newsletters	E – n/a
Other	F – n/a
Labels and Labeling	G

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing to market Deoxycholic acid in a carton containing four 2 mL vials. This packaging presentation would allow for a maximum dose of 8 mL, which is less than the maximum dose per session (i.e. 10 mL); therefore, it seems reasonable.

We note that the proprietary name, established name, dosage form and strength statements are not presented together in consecutive lines and does not follow the standard practice. In addition, the container label for the sample vial does not include the route of administration. Also, the color scheme of the carton labeling makes use of (b) (4) font over orange background, which makes it difficult to read. Finally, the carton labeling lacks the statement “Single-use vial; discard unused portion”.

## 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed packaging configuration is adequate. However, DMEPA recommends the following container labels and carton labeling comments be implemented prior to approval of this application.

## 4.1 RECOMMENDATIONS FOR KYTHERA BIOPHARMACEUTICALS

### A. General Comments

- 1- Revise the presentation of the proprietary name, established name, dosage form and strength on every panel to read:

Tradename  
(deoxycholic acid) Injection  
20 mg/2 mL  
(10 mg/mL)

- 2- The strength statements should be presented using the same font size as the established name and dosage form.

### B. Container Labels (sample)

1. Include the route of administration statement “for subcutaneous use”. To achieve this you may reduce the size of the sample statement or shorten the sample statement to read “Sample”.

### C. Carton Labeling

1. Consider revising your color scheme. As currently presented, the (b) (4) font letters over the color background is difficult to read.
2. Relocate the sample statement to the bottom of the principal display panel. As currently presented, the samples statement is more prominent than more relevant information on the labels. Also, add another sample statement to the back panel.
3. Include the statement “Single-use vials. Discard unused portion.”
4. Relocate the route of administration statement “for subcutaneous use” so that it does not intervene between the dosage form and strength statements, as these should be presented together (see General Comment 1).

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Deoxycholic Acid that Kythera Biopharmaceuticals submitted on May 13, 2014.

<b>Table 2. Relevant Product Information for Deoxycholic Acid</b>	
<b>Initial Approval Date</b>	n/a
<b>Active Ingredient</b>	Deoxycholic Acid
<b>Indication</b>	Improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.
<b>Route of Administration</b>	Subcutaneous
<b>Dosage Form</b>	Injection
<b>Strength</b>	20 mg/2 mL (10 mg/mL)
<b>Dose and Frequency</b>	<ul style="list-style-type: none"><li>• 0.2 mL injected into subcutaneous fat tissue in the submental area, 1 cm apart until all sites in the planned treatment area have been injected.</li><li>• Up to 50 injections or 10 mL may be injected in a single treatment.</li><li>• Up to six single treatments may be administered at intervals no less than 4-weeks apart.</li></ul>
<b>How Supplied</b>	Pack of four 2 mL vials
<b>Storage</b>	Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F).
<b>Container Closure</b>	n/a

## **APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

N/A

## **APPENDIX C. PREVIOUS DMEPA REVIEWS**

### **C.1 Methods**

We searched the L: drive on November 25, 2014 using the terms, Deoxycholic Acid to identify reviews previously performed by DMEPA.

### **C.2 Results**

Our search did not identify any previous reviews relevant to labels and labeling.

## **APPENDIX D. HUMAN FACTORS STUDY**

N/A

## **APPENDIX E. ISMP NEWSLETTERS**

N/A

## **APPENDIX F. N/A**

N/A

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarket medication error data, we reviewed the following Deoxycholic Acid labels and labeling submitted by Kythera Biopharmaceuticals on May 13, 2014.

- Container label
- Carton labeling

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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CARLOS M MENA-GRILLASCA  
12/04/2014

KENDRA C WORTHY  
12/08/2014

ATX-101 (REFINE)  
NDA 206333  
Kythera Biopharmaceuticals

**OFFICE OF DEVICE EVALUATION**  
**Inter-center Consultative Review**  
**(NDA 206333)**

---

**From:** Anjum Khan, M.D., MPH (email: [anjum.khan@fda.hhs.gov](mailto:anjum.khan@fda.hhs.gov))  
ENTB/DONED/ODE/CDRH

Janette Alexander, MD  
PRSBI/DSD/CDRH

**To:** Milena Lolic, M.D.  
Division of Dermatology and Dental products (DDDP)  
CDER

**Cc:** Eric Mann, M.D. Ph.D.  
Clinical Deputy Director, DONED/ODE/CDRH

**Cc:** Srinivas Nandkumar, PhD  
Branch Chief, ENTB/DONED/ODE/CDRH

**Subject:** **NDA 206333**  
**ATX 101-11-22**  
(1% Deoxycholic acid injection)

**Date:** October 23, 2014

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**Purpose:**

This memo includes a focused review of new NME NDA-206333 for ATX-101 for submental fat reduction as it pertains to safety issues associated with administration of ATX-101(1% Deoxycholic acid) injection technique and to mitigate risk of nerve or other injuries. There have been two trials conducted in Phase III of the study.

This memo includes review of adverse events of marginal mandibular nerve; dysphagia and dysphonia observed during the Phase III trial and specific recommendations/ comments/edits to the proposed labeling to mitigate risk of marginal mandibular nerve injury.

This document reproduces sections of concern in the current labeling submitted by the sponsor as it relates to Injection technique of ATX-101 and avoidance of marginal mandibular nerve injury. The reviewer comments/recommendations as addressed for each pertinent section will appear in color.

(b) (4)

[Redacted]

**Indications for Use:**

ATX-101 is (b) (4) indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

**Dosage and Administration (Section-2, labeling):**

(b) (4)

[Redacted]

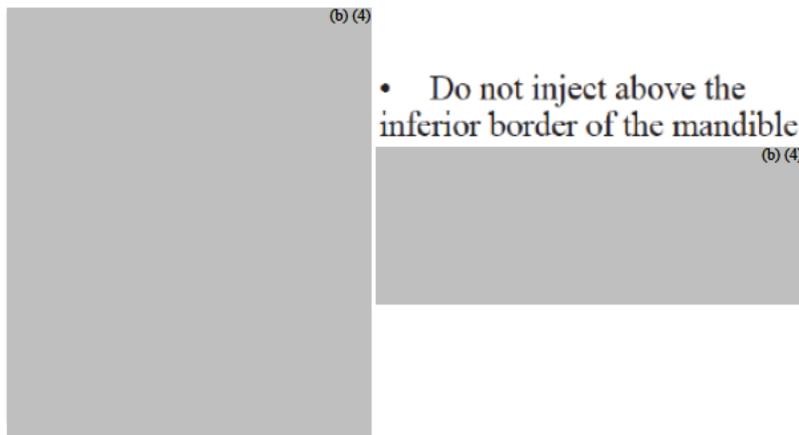
*Reviewer Comment: The section of Dosage and Administration (Section 2) needs to [REDACTED] (b) (4) Also the last statement that states “Careful consideration should be given to use of ATX-101™ in patients with excessive skin laxity, prominent platysmal bands or other conditions for which reduction of submental fat may result in an aesthetically undesirable outcome” should also be included under precautions as well as under the description of Injection Technique*

**Injection Technique (Section 2.1 of labeling):**

In this section, sponsor describes the following “Health care professionals administering ATX-101™ must understand the relevant submental anatomy and associated neuromuscular structures in the area involved and any alterations to the anatomy due to prior surgical or aesthetic procedures [see Warnings and Precautions (5)]. Needle placement is very important. [REDACTED] (b) (4)



**Figure 1. Avoid the Marginal Mandibular Nerve Area**



*Reviewer Comment: Under Injection Technique (Section 2.1), Sponsor’s states that “Do not inject above the inferior border of the mandible [REDACTED] (b) (4)*

ATX-101 (REFINE)

NDA 206333

Kythera Biopharmaceuticals

(b) (4)

(b) (4)

(b) (4)

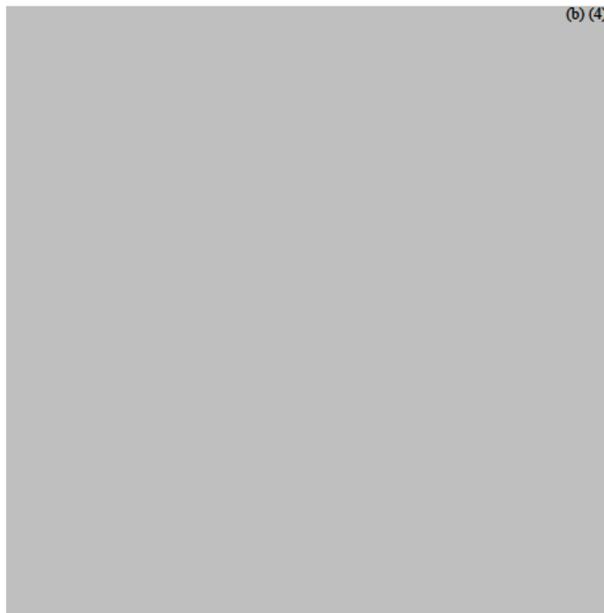


*To avoid marginal mandibular nerve area, the injections need to be 1-1.5 cm below the inferior border of the mandible from the angle of the mandible to the mentum. Therefore, we recommend that modification be made to the statement regarding the instruction for injections below the mandible as well as to the Figure to reflect the entire area below the mandible that must be avoided as follows:*

(b) (4)



(b) (4)



- Palpate the submental area to identify subcutaneous fat between the dermis and platysma (pre-platysmal fat) [REDACTED] (b) (4) (Figure 2).

## Figure 2. Sagittal View of Platysma Area



- Use of ice/cold packs, topical and /or injectable local anesthetic (e.g., lidocaine) [REDACTED] (b) (4) enhance patient comfort
- The planned treatment area is to be marked out with a surgical pen using a 1cm grid to mark the injection sites (Figure-3)

**Figure 3.**



***Reviewer Comment:***

[Redacted text block]

*Because the course of the marginal mandibular nerve is variable in its relationship to the lower border of the mandible (totally above, totally below (more frequent) or both above and below), it is critical that clear instruction be given for the superior and posterior extent of the treatment area. The marginal mandibular nerve (MMN) is vulnerable in two places as it courses its way after originating from the facial nerve trunk. The first site of vulnerability is as the nerve wraps around the facial vein at the angle of the mandible and second when it dips and becomes superficial after traversing underneath the platysma muscle as it courses toward the mentum. It is recommended*

[Redacted text block]

[REDACTED] (b) (4)

[REDACTED] (b) (4)

**Injection Technique Continued:**

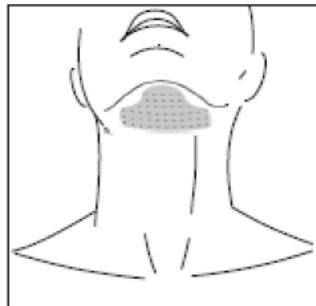
Under injection technique (Section 2.1 of labeling), sponsor states “That the planned treatment is marked out with a surgical pen using a 1 cm grid to mark the injection site.” In response to a specific question regarding the grid use, sponsor states that:

“ [REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4)

**Treatment Area and Injection <sup>(b) (4)</sup> Pattern**



■ Treatment Area  
⋮ Injection Grid Marks

*Reviewer Comment: We agree that use of grid will be helpful to the user in spacing the injections.* (b) (4)

*. Therefore, we believe that the Instructions for Use clearly define the limitations of the planned treatment area. For e.g., the planned treatment area must be limited superiorly to 1-1.5 cm below the mandible margin in its entire length and inferiorly to the level of thyroid notch. If there is a limitation to the lateral boundary, it should also be clearly defined. In addition, a comment should be added under the section of warnings to state that “Do not inject ATX-101 outside the defined parameters”* (b) (4)

Using a large bore needle, draw 1 mL of **ATX-101**<sup>TM</sup> into a sterile 1 mL syringe and expel any air bubbles in the syringe barrel. Using a 30 gauge (or smaller) 0.5-inch needle, (b) (4)

Avoid injecting into the post-platysmal fat (Figure 2). (b) (4)

(b) (4) Avoid injecting into other tissues such as the muscle, salivary glands and lymph nodes.

(b) (4)

Prior to each treatment session, (b) (4) submental area to ensure sufficient SMF (b) (4)

(b) (4)

*Reviewer Comment: The injection technique described above is satisfactory. For easier reading perhaps the description can be presented in numbered steps or bulleted format.*

## WARNINGS AND PRECAUTIONS (Section 5)

(b) (4) (5.1):

(b) (4)

(b) (4)

(b) (4)

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

*Reviewer Comment: We recommend* [REDACTED] (b) (4)

[REDACTED] (b) (4) (Section 5.1):

[REDACTED] (b) (4)

**Patient Information:**

**What are the possible side effects of ATX-101TM?**

[REDACTED] (b) (4) bruising, pain, numbness, swelling, redness, [REDACTED] (b) (4)  
[REDACTED] (b) (4) areas of hardness, [REDACTED] (b) (4) around the treatment area. [REDACTED] (b) (4)

[REDACTED]

*Reviewer Comment: We acknowledge that the rate of adverse events of mandibular nerve injury, difficulty swallowing, and [REDACTED] (b) (4) observed in the*

*many trials conducted for ATX-101 was small and all resolved. However, such adverse events are more disturbing to the patients. Therefore, we recommend*

(b) (4)

### **Conclusion/Recommendations:**

Thank you for asking us to review the labeling as it pertains to avoiding injury to the marginal mandibular nerve in the use of ATX-101 for the treatment of submental fat.

We recommend that following revisions/modifications be made to the Instructions for Use as it pertains to the safe injections of ATX in the submental area and possibly to avoid injury to the marginal mandibular injury:

1. In Section 2.1 of the labeling, you describe the injection technique. Please address the following issues regarding the injection technique:

a) In Section 2.1, you describe the following “Health care professionals administering **ATX-101**<sup>TM</sup> must understand the relevant submental anatomy and associated neuromuscular structures in the area involved and any alterations to the anatomy due to prior surgical or aesthetic procedures [see *Warnings and Precautions (5)*]. Needle placement is very important

(b) (4)

(b) (4)

(b) (4) We find this statement

as well as Figure-1 very confusing. For clarity of understanding, we recommend that this section be revised, both in text and the figure. For e.g., the following language would be clearer:

[REDACTED] (b) (4)

ii) You can retain the instruction that states “Do not inject above the

[REDACTED] (b) (4)

[REDACTED] (b) (4)

2. [REDACTED] (b) (4)

Because the course of the marginal mandibular nerve is variable in its relationship to the lower border of the mandible (totally above, totally below (more frequent) or both above and below), it is critical that clear instruction be given for the superior and posterior extent of the treatment area as described in #1 above. The marginal mandibular nerve (MMN) is vulnerable in two places as it courses its way after originating from the facial nerve trunk. The first site of vulnerability is as the nerve wraps around the facial vein at the angle of the mandible and second when it dips and becomes superficial after traversing underneath the platysma muscle as

it courses toward the mentum. We recommend

(b) (4)

(b) (4)

(b) (4)

3. Under injection technique (Section 2.1 of labeling), you state “That the planned treatment is marked out with a surgical pen using a 1 cm grid to mark the injection site.” In response to a specific question regarding the grid use, you further state that

(b) (4)

(b) (4)

(b) (4)

[REDACTED] (b) (4)

We agree that use of grid will be helpful to the user in spacing the injections.

[REDACTED] (b) (4)

. Therefore, we recommend that the Instructions for Use clearly define the limitations of the planned treatment area. For e.g., the planned treatment area must be limited superiorly to 1-1.5 cm below the mandible margin in its entire length and inferiorly to the level of thyroid notch. If there is a limitation to the lateral boundary, it should also be clearly defined. In addition, a comment should be added under warnings to state that “Do not inject ATX-101 outside the defined parameters” [REDACTED] (b) (4)

[REDACTED] (b) (4)

4. In the Section of Warnings and Precautions- [REDACTED] (b) (4)  
(Section 5.1) [REDACTED] (b) (4)

[REDACTED] We recommend you consider adding three additional comments to this section as listed below:

[REDACTED] (b) (4)

5. In the patient information brochure, under what are the possible side effects of ATX-101 you describe events like bruising, pain, numbness, swelling, etc. You also state that “ (b) (4)

.” We acknowledge that the rate of adverse events of mandibular nerve injury, difficulty swallowing, and  (b) (4) observed in the many trials conducted for ATX-101 was small and all resolved. However, such adverse events are more disturbing to the patients. Therefore, we recommend  (b) (4)

6. In the Section of Dosage and administration (Section-2, labeling), you describe how ATX-101 is supplied for use (single use vials of 2mL of a 10mg/mL), and the condition of laxity that necessitates careful use. However, this section does not include a clear instruction of what is a maximal allowable dose. We recommend you include a statement in this section that clearly states that 100mg (10ml or 50 injections) is a maximal allowable dose in a single treatment session. In addition, the last statement that states “Careful consideration should be given to use of ATX-101<sup>TM</sup> in patients with excessive skin laxity, prominent platysmal bands or other conditions for which reduction of submental fat may result in an aesthetically undesirable outcome” should additionally be included under precautions as well as under the description of Injection Technique besides this section of Dosage and administration.

Anjum Khan, MD, MPH

ENTB/DOED/ODE

Anjum Khan -S

Digitally signed by Anjum Khan -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Anjum Khan -S,  
0.9.2342.19200300.100.1.1=1300132807  
Date: 2014.11.14 21:38:17 -05'00'

Janette Alexander, MD

PRsBI/DSD/CDRH



Janette Alexander -S  
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-05'00'

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/s/  
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MATTHEW E WHITE

11/19/2014

CDRH review entered into DARRTS on behalf of Dr. Anjum Khan and Dr. Janette Alexander

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 206333	NDA Supplement #-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: (deoxycholic acid) Dosage Form: Injection Strengths: 10 mg/mL		
Applicant: Kythera Biopharmaceuticals, Inc.		
Date of Application: 5/13/2014 Date of Receipt: 5/13/2014 Date clock started after UN:		
PDUFA Goal Date: 5/13/2015	Action Goal Date (if different):	
Filing Date: 7/11/2014	Date of Filing Meeting: 6/25/2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 - NME		
Proposed indication(s)/Proposed change(s): For improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</b></i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of BLA  <i><b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b></i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</b></i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 079726				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input checked="" type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested: 5  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For BLAs:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Format and Content</b>	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?	

<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b>  <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b>  <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b><u>Proprietary Name</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Request submitted 5/23/2014
<b><u>REMS</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b><u>Prescription Labeling</u></b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 4/20/2011	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 11/13/2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 12/16/2011	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** June 25, 2014

**NDA 206333**

**PROPRIETARY NAME:**

**ESTABLISHED/PROPER NAME:** (deoxycholic acid)

**DOSAGE FORM/STRENGTH:** Injection, 10 mg/mL

**APPLICANT:** Kythera Biopharmaceuticals, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** For improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

**BACKGROUND:** New NME NDA received May 13, 2014. Application to be reviewed under “The Program”

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matthew White	Y
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	David Kettl		Y
Clinical	Reviewer:	Milena Lolic	Y
	TL:	David Kettl	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	An-Chi Lu	Y
	TL:	Doanh Tran (Chinmay Shukla covering)	Y
Biostatistics	Reviewer:	Kathleen Fritsch	N
	TL:	Mohamed Alesh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jill Merrill	Y
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for BLAs/BLA efficacy supplements)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	Y
	TL:	Shulin Ding	Y
Quality Microbiology <i>(for sterile products)</i>	Reviewer:	Erika Pfeiler	Y
	TL:	Brian Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Christina Capacci-Daniel	Y
	TL:	David Doleski	N
OSE/DMEPA (proprietary name)	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	Nyedra Booker	Y
	TL:	Jamie Wilkins Parker	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	DPV: Jessica Weintraub/Ida-Lina Diak DEPI: Sukhminder Sandhu		Y N
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? <input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO</li> <li>Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <input type="checkbox"/> YES <input type="checkbox"/> NO</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation? <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</li> </ul> <p><b>If no, explain:</b></p>	
<ul style="list-style-type: none"> <li>Electronic Submission comments <p><b>List comments:</b></p> </li> </ul>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed? <p><b>If no, explain:</b></p> </li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: TBD <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: New NME NDA
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b> Review issues for 74-day letter</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Dr. Julie Beitz</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:  <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	Other

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MATTHEW E WHITE  
07/01/2014

BARBARA J GOULD  
07/02/2014

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 206333

**Application Type:** New NDA

**Name of Drug/Dosage Form:** Kybella™ (deoxycholic acid) injection, 10 mg/mL

**Applicant:** Kythera Biopharmaceuticals, Inc.

**Receipt Date:** 5/13/2014

**Goal Date:** 5/13/2015

## 1. Regulatory History and Applicant's Main Proposals

Kythera Biopharmaceuticals, Inc. submitted an original NDA for Kybella™ (deoxycholic acid) injection, 10 mg/mL for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults. In regards to the NDA content and completeness of data submitted, there was an agreement made in a pre-NDA meeting held between the Agency and Kythera Biopharmaceuticals, Inc. on November 13, 2013. As per the agreement, there will be additional drug product and drug substance stability data that will be submitted to the agency 30 days following the original NDA submission.

Pre-NDA meeting: 11/13/2013

EoP2 meeting: 4/20/11

SPA agreement: 12/16/11

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. In the HL, "Dosage Forms" is not plural in the heading "Dosage Forms and Strengths"

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 25, 2014. The resubmitted PI will be used for further labeling review.

## Appendix

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The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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### Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

#### HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.  
***Comment:*** *The margins on each side of the highlight is 1 inch and it should be 1/2 inch.*
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.  
***Instructions to complete this item:*** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.  
***Comment:***
- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.  
***Comment:*** *There is no horizontal line to separate TOC from the FPI. The horizontal line between HL and TOC should be a single continuous horizontal line that spans the width of the page without any breaks.*
- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.  
***Comment:*** *Header titles should be centered in the columns; the horizontal lines on either side of the header titles should be created using the “hyphen” function not the “underline” function; the horizontal lines on either side of the section header titles should extend all the way to both the left and right margin of the columns.*
- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.  
***Comment:*** *There is white space between the HL Heading and HL Limitation Statement. There is white space between the product title and Initial U.S. Approval.*
- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.  
***Comment:*** *Not all statements and topics in HL have references.*
- YES** 7. Section headings must be presented in the following order in HL:

## Selected Requirements of Prescribing Information

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

**Comment:** Add "XXXX" as place holder

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

**Comment:**

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

**Comment:**

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

**Comment:**

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

**Comment:**

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

**Comment:**

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:**

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:**

### Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

**Comment:**

### Contraindications in Highlights

## Selected Requirements of Prescribing Information

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

**Comment:** *Correct product name*

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

**Comment:**

### Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

**Comment:** *Remove brackets from “[and FDA-approved Patient Labeling]”*

### Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

**Comment:** *The word “Revised” should be spelled out.*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:** *References should cite the section header not the subsection header. Correct cross-references in sections 7, 8.1, and 13.1*

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

***Comment:*** *As instructed in the guidance for industry "Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products--Content and Format", the statement instructing prescribers to advise patients to read the patient labeling should appear as the first statement in section 17. Also the current statement should be revised to read as follows: "Advise the patient to read the FDA-approved patient labeling (Patient Information)."*

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

[text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MATTHEW E WHITE  
06/30/2014